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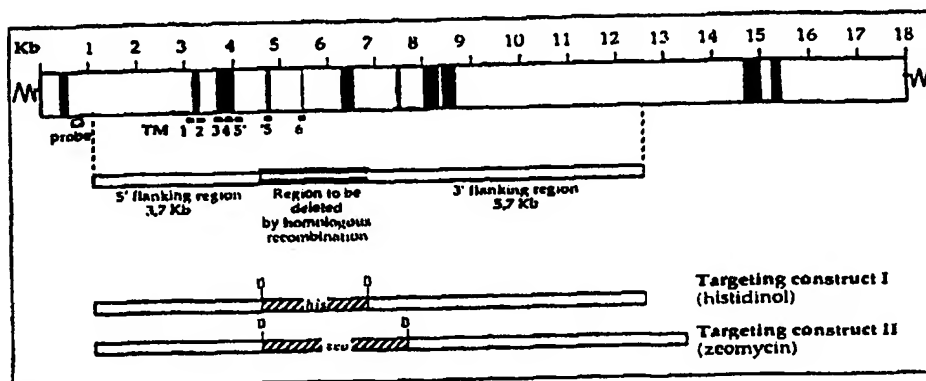
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(54) Title: CHARACTERIZATION OF A CALCIUM CHANNEL FAMILY



(57) Abstract

Nucleic acids encoding SOC/CRAC calcium channel polypeptides, including fragments and biologically functional variants thereof and encoded polypeptides are provided. The nucleic acids and polypeptides disclosed herein are useful as therapeutic and diagnostic agents. Agents that selectively bind to the foregoing polypeptides and genes also are provided.

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CHARACTERIZATION OF A CALCIUM CHANNEL FAMILY**Field of the Invention**

This invention relates to nucleic acids coding for a novel family of calcium channel polypeptides, the encoded polypeptides, unique fragments of the foregoing, and methods of making and using same.

Background of the Invention

Calcium channels are membrane-spanning, multi-subunit proteins that facilitate the controlled transport ("flux") of Ca^{2+} ions into and out of cells. Cells throughout the animal kingdom, and at least some bacterial, fungal and plant cells, possess one or more types of calcium channels. In general, "excitable" cells, such as neurons of the central nervous system, peripheral nerve cells, and muscle cells, including those of skeletal muscles, cardiac muscles, and venous and arterial smooth muscles, possess voltage-dependent calcium channels. In a voltage-dependent calcium channel, the transport of Ca^{2+} ions into and out of the cells requires a certain minimal level of depolarization (the difference in potential between the inside of the cell bearing the channel and the extracellular environment) with the rate of Ca^{2+} cell flux dependent on the difference in potential. In "non-excitable" cells, calcium influx is thought to occur predominantly in response to stimuli which cause the release of calcium from intracellular stores. This process, termed *store operated calcium influx*, is not well understood.

Characterization of a particular type of calcium channel by analysis of whole cells is complicated by the presence of mixed populations of different types of calcium channels in the majority of cells. Although single-channel recording methods can be used to examine individual calcium channels, such analysis does not reveal information related to the molecular structure or biochemical composition of the channel. Furthermore, in this type of analysis, the channel is isolated from other cellular constituents that might be important for the channel's natural functions and pharmacological interactions. To study the calcium channel structure-function relationship, large amounts of pure channel protein are needed. However, acquiring large amounts of pure protein is difficult in view of the complex nature of these multisubunit proteins, the varying concentrations of calcium channel proteins in tissue sources, the presence of mixed populations of calcium channel proteins in tissues, and the modifications of the native protein that can occur during the isolation procedure.

Summary of the Invention

The invention is based on the identification of a novel family of calcium channel polypeptides and the molecular cloning and partial characterization of a novel member of this family that is expressed predominantly in human hematopoietic cells, liver, and kidney. This newly identified family of calcium channel polypeptides is designated, "SOC" or "CRAC" or "ICRAC", for Store Operated Channels or Calcium Release Activated Channels. Although not wishing to be bound to any particular theory or mechanism, it is believed that the SOC/CRAC calcium channel polypeptides are transmembrane polypeptides that modulate Ca^{2+} flux "into" and "out of" a cell, for example, in certain instances they may be activated upon depletion of Ca^{2+} from intracellular calcium stores, allowing Ca^{2+} influx into the cell. Accordingly, the compositions disclosed herein are believed to be useful for modulating calcium transport into and out of such intracellular stores and for the treatment of disorders that are characterized by aberrant calcium transport into and out of such intracellular stores. In particular, we believe that the SOC/CRAC calcium channel polypeptides disclosed herein play an important role in the influx of extracellular calcium by mediating the refilling of intracellular calcium stores following their depletion. Accordingly, we believe that the compositions for expressing functional SOC/CRAC calcium channel polypeptides in cells, as disclosed herein, are useful for treating patients having conditions that are characterized by reduced extracellular calcium influx into their SOC/CRAC-expressing cells. Additionally, the compositions of the invention are useful for delivering therapeutic and/or imaging agents to cells which preferentially express SOC/CRAC calcium channel polypeptides and, in particular, for delivering such agents to hematopoietic cells, liver, heart, spleen, and kidney to modulate proliferation and growth of these cells. Moreover, in view of the importance of cellular calcium levels to cell viability, we believe that SOC-2/CRAC-1, SOC-3/CRAC-2, and SOC-4/CRAC-3 as disclosed herein, and/or other members of the SOC/CRAC family of calcium channel polypeptides, represent an ideal target for designing and/or identifying (e.g., from molecular libraries) small molecule inhibitors that block lymphocyte proliferation, as well as other binding agents that selectively bind to SOC/CRAC polypeptides to which drugs or toxins can be conjugated for delivery to SOC/CRAC polypeptide expressing cells.

The invention is based, in part, on the molecular cloning and sequence analysis of the novel SOC/CRAC calcium channel molecules disclosed herein (also referred to as a "SOC-2/CRAC-1 molecule," a "SOC-3/CRAC-2 molecule," and/or "SOC-4/CRAC-3 molecule") that are predominantly expressed in human hematopoietic cells, liver, spleen, heart, and

kidney (SOC-2/CRAC-1), kidney and colon (SOC-3/CRAC-2), and prostate (SOC-4/CRAC-3 molecule). As used herein, a "SOC/CRAC molecule" embraces a "SOC/CRAC calcium channel nucleic acid" (or "SOC/CRAC nucleic acid") and a "SOC/CRAC calcium channel polypeptide" (or "SOC/CRAC polypeptide"). Homologs and alleles also are embraced within the meaning of a SOC/CRAC calcium channel molecule.

According to one aspect of the invention, isolated SOC/CRAC nucleic acids which code for one or more member(s) of the SOC/CRAC family of calcium channel polypeptides or unique fragments thereof are provided. The isolated nucleic acids refer to one or more of the following:

(a) nucleic acid molecules which hybridize under stringent conditions to a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, and which code for a SOC/CRAC polypeptide;

(b) deletions, additions and substitutions of (a) which code for a respective SOC/CRAC polypeptide;

(c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) in codon sequence due to the degeneracy of the genetic code, and

(d) complements of (a), (b) or (c).

The invention in another aspect provides an isolated nucleic acid molecule selected from the group consisting of (a) a unique fragment of a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:29, and SEQ ID NO:31, (b) complements of (a), provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to any sequence selected from a sequence group consisting of (1) sequences having the SEQ. ID NOS. or GenBank accession numbers of Table I, (2) complements of (1), and (3) fragments of (1) and (2).

According to yet another aspect of the invention, isolated SOC/CRAC polypeptides are provided. The isolated SOC/CRAC polypeptide molecules are encoded by one or more SOC/CRAC nucleic acid molecules of the invention. Preferably, the SOC/CRAC polypeptide contains one or more polypeptides selected from the group consisting of the polypeptides having SEQ. ID Nos. 2, 4, 6, 8, 24, 26, 28, 30, and 32. In other embodiments, the isolated polypeptide may be a fragment or variant of the foregoing SOC/CRAC polypeptide molecules of sufficient length to represent a sequence unique within the human genome, and identifying

with a polypeptide that functions as a calcium channel, provided that the fragment excludes a sequence of contiguous amino acids identified in Table II, and/or excludes a sequence of contiguous amino acids encoded for by a nucleic acid sequence identified in Table I. In another embodiment, immunogenic fragments of the polypeptide molecules described above are provided.

According to another aspect of the invention, isolated SOC/CRAC binding agents (e.g., polypeptides) are provided which selectively bind to a SOC/CRAC molecule (e.g., a SOC/CRAC polypeptide encoded by the isolated nucleic acid molecules of the invention). Preferably, the isolated binding agents selectively bind to a polypeptide which comprises the sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32, or unique fragments thereof. In the preferred embodiments, the isolated binding polypeptides include antibodies and fragments of antibodies (e.g., Fab, F(ab)₂, Fd and antibody fragments which include a CDR3 region which binds selectively to a SOC/CRAC polypeptide). Preferably, the antibodies for human therapeutic applications are human antibodies.

According to another aspect of the invention, a pharmaceutical composition containing a pharmaceutically effective amount of an isolated SOC/CRAC nucleic acid, an isolated SOC/CRAC polypeptide, or an isolated SOC/CRAC binding polypeptide in a pharmaceutically acceptable carrier also is provided. The pharmaceutical compositions are useful in accordance with therapeutic methods disclosed herein.

According to yet another aspect of the invention, a method for isolating a SOC/CRAC molecule is provided. The method involves:

a) contacting a SOC/CRAC nucleic acid or a SOC/CRAC binding polypeptide with a sample that is believed to contain one or more SOC/CRAC molecules, under conditions to form a complex of the SOC/CRAC nucleic acid or the SOC/CRAC binding polypeptide and the SOC/CRAC molecule;

b) detecting the presence of the complex;

c) isolating the SOC/CRAC molecule from the complex; and

d) determining whether the isolated SOC/CRAC molecule has SOC/CRAC calcium channel activity. As used herein "SOC/CRAC calcium channel activity" refers to the transport of Ca²⁺ into and out of intracellular stores that is mediated by a SOC/CRAC

polypeptide. In general, the SOC/CRAC calcium channel activity is initiated by a reduction or depletion of intracellular calcium stores.

In certain embodiments, the SOC/CRAC nucleic acid is a SOC-2/CRAC-1 nucleic acid (e.g., a nucleic acid having SEQ. ID NO. 27, or complements thereof); in certain other
5 embodiments, the SOC/CRAC nucleic acid is a SOC-3/CRAC-2 nucleic acid (e.g., a nucleic acid having SEQ. ID NO. 29, or complements thereof); in further embodiments, the SOC/CRAC nucleic acid is a SOC-4/CRAC-3 nucleic acid (e.g., a nucleic acid having SEQ. ID NO. 31, or complements thereof). In yet other embodiments, the SOC/CRAC polypeptide
10 is a SOC-2/CRAC-1 binding polypeptide (e.g., an antibody that selectively binds to a SOC-2/CRAC-1 polypeptide). In yet further embodiments, the SOC/CRAC polypeptide is a SOC-3/CRAC-2 binding polypeptide (e.g., an antibody that selectively binds to a SOC-3/CRAC-2 polypeptide). In some embodiments, the SOC/CRAC polypeptide is a SOC-4/CRAC-3 binding polypeptide (e.g., an antibody that selectively binds to a SOC-4/CRAC-3 polypeptide). In the preferred embodiments, the isolated binding polypeptides include
15 antibodies and fragments of antibodies (e.g., Fab, F(ab)₂, Fd and antibody fragments which include a CDR3 region which binds selectively to a SOC-2/CRAC-1, to a SOC-3/CRAC-2, and/or to a SOC-4/CRAC-3 polypeptide). Preferably the isolated binding polypeptides or other binding agents selectively bind to a single SOC/CRAC molecule, i.e., are capable of distinguishing between different members of the SOC/CRAC family. Accordingly, one or
20 more SOC/CRAC binding agents can be contained in a single composition (e.g., a pharmaceutical composition) to identify multiple SOC/CRAC molecules *in vivo* or *in vitro*.

According to yet another aspect of the invention, a method for identifying agents useful in the modulation of SOC/CRAC calcium channel activity is provided. The method involves:

- 25 a) contacting a SOC/CRAC polypeptide with a candidate agent suspected of modulating SOC/CRAC calcium channel activity, under conditions sufficient to allow the candidate agent to interact selectively with (e.g. bind to) the SOC/CRAC polypeptide;
- b) detecting a Ca²⁺ concentration of step (b) associated with the SOC/CRAC calcium channel activity of the SOC/CRAC polypeptide in the presence of the candidate agent; and
- 30 c) comparing the Ca²⁺ concentration of step (b) with a control Ca²⁺ concentration of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the candidate agent modulates (increases or decreases) SOC/CRAC calcium channel activity.

According to another aspect of the invention, a method for identifying agents useful in the modulation of a SOC/CRAC polypeptide kinase activity is provided. The method involves:

5 a) contacting a SOC/CRAC polypeptide with kinase activity with a candidate agent suspected of modulating SOC/CRAC kinase activity, under conditions sufficient to allow the candidate agent to interact with the SOC/CRAC polypeptide and modulate its kinase activity;

b) detecting a kinase activity associated with the SOC/CRAC polypeptide in the presence of the candidate agent; and

10 c) comparing the kinase activity of step (b) with a control kinase activity of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the candidate agent modulates (increases or decreases) SOC/CRAC kinase activity. In some embodiments the SOC/CRAC polypeptide comprises amino acids 999-1180 of the SOC-2/CRAC-1 polypeptide (SEQ ID NO:24), or a fragment thereof that retains the kinase activity.

15 According to yet another aspect of the invention, a method for determining the level of expression of a SOC/CRAC polypeptide in a subject is provided. The method involves:

a) measuring the expression of a SOC/CRAC polypeptide in a test sample, and

20 b) comparing the measured expression of the SOC/CRAC polypeptide in the test sample to the expression of a SOC/CRAC polypeptide in a control containing a known level of expression to determine the level of SOC/CRAC expression in the subject. Expression is defined as SOC/CRAC mRNA expression or SOC/CRAC polypeptide expression. Various methods can be used to measure expression. The preferred embodiments of the invention utilize PCR and Northern blotting for measuring mRNA expression, and monoclonal or polyclonal SOC/CRAC antisera as reagents for measuring SOC/CRAC polypeptide expression. In preferred embodiments, the SOC/CRAC molecule (nucleic acid and/or
25 polypeptide) is SOC-2/CRAC-1. In other preferred embodiments, the SOC/CRAC molecule is SOC-3/CRAC-2. In yet further preferred embodiments, the SOC/CRAC molecule is SOC-4/CRAC-3. In certain embodiments, the test samples include biopsy samples and biological fluids such as blood. The method is useful, e.g., for assessing the presence or absence or stage of a proliferative disorder in a subject.

30 The invention also contemplates kits comprising a package including assays for SOC/CRAC epitopes, SOC/CRAC nucleic acids, and instructions, and optionally related materials such as controls, for example, a number, color chart, or an epitope of the expression product of the foregoing isolated nucleic acid molecules of the invention for comparing, for

example, the level of SOC/CRAC polypeptides or SOC/CRAC nucleic acid forms (wild-type or mutant) in a test sample to the level in a control sample having a known amount of a SOC/CRAC nucleic acid or SOC/CRAC polypeptide. This comparison can be used to assess in a subject a risk of developing a cancer or the progression of a cancer. The kits may also include assays for other known genes, and expression products thereof, associated with, for example, proliferative disorders (e.g., BRCA, p53, etc.). In a preferred embodiment, the kit comprises a package containing: (a) a binding agent that selectively binds to an isolated nucleic acid of the invention or an expression product thereof to obtain a measured test value, (b) a control containing a known amount of a SOC/CRAC nucleic acid or a SOC/CRAC polypeptide to obtain a measured control value, and (c) instructions for comparing the measured test value to the measured control value to determine the amount of SOC/CRAC nucleic acid or expression product thereof in a sample.

The invention provides isolated nucleic acid molecules, unique fragments thereof, expression vectors containing the foregoing, and host cells containing the foregoing. The invention also provides isolated binding polypeptides and binding agents which bind such polypeptides, including antibodies, and pharmaceutical compositions containing any of the compositions of the invention. The foregoing can be used, *inter alia*, in the diagnosis or treatment of conditions characterized by the aberrant expression levels and/or the presence of mutant forms of a SOC/CRAC nucleic acid or polypeptide. The invention also provides methods for identifying agents that alter the function of the SOC/CRAC polypeptide.

These and other aspects of the invention, as well as various advantages and utilities, will be more apparent with reference to the detailed description of the preferred embodiments.

Brief Description of the Sequences

SEQ ID NO:1 is a partial nucleotide sequence of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:2 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:1).

SEQ ID NO:3 is a partial nucleotide sequence of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:4 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:3).

SEQ ID NO:5 is a partial nucleotide sequence of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:6 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:5).

-8-

SEQ ID NO:7 is a partial nucleotide sequence of the mouse homologue (mSOC-2/CRAC-1) of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:8 is the predicted amino acid sequence of the translation product of the mSOC-2/CRAC-1 cDNA (SEQ ID NO:7).

5 SEQ ID NO:9 is the nucleotide sequence of the mouse MLSN-1 (SOC-1) cDNA.

SEQ ID NO:10 is the predicted amino acid sequence of the translation product of the mouse MLSN-1 (SOC-1) cDNA (SEQ ID NO:9).

SEQ ID NO:11 is the nucleotide sequence of a human calcium channel cDNA with GenBank Acc. no.: AB001535.

10 SEQ ID NO:12 is the predicted amino acid sequence of the translation product of the human calcium channel cDNA with GenBank Acc. no.: AB001535 (SEQ ID NO:11).

SEQ ID NO:13 is the amino acid sequence of a *C. Elegans* polypeptide at the c05c12.3 locus.

15 SEQ ID NO:14 is the amino acid sequence of a *C. Elegans* polypeptide at the F54D1 locus.

SEQ ID NO:15 is the amino acid sequence of a *C. Elegans* polypeptide at the t01H8 locus.

SEQ ID NO:16 is the nucleotide sequence of a mouse kidney cDNA with GenBank Acc. no.: AI226731.

20 SEQ ID NO:17 is the predicted amino acid sequence of the translation product of the mouse kidney cDNA with GenBank Acc. no.: AI226731 (SEQ ID NO:16).

SEQ ID NO:18 is the nucleotide sequence of a human brain cDNA with GenBank Acc. no.: H18835.

25 SEQ ID NO:19 is the predicted amino acid sequence of the translation product of the human brain cDNA with GenBank Acc. no.: H18835 (SEQ ID NO:18).

SEQ ID NO:20 is the nucleotide sequence of the human EST with GenBank Acc. no.: AA419592.

SEQ ID NO:21 is the nucleotide sequence of the human EST with GenBank Acc. no.: AA419407.

30 SEQ ID NO:22 is the nucleotide sequence of the mouse EST with GenBank Acc. no.: AI098310.

SEQ ID NO:23 is a partial nucleotide sequence of the human SOC-2/CRAC-1 cDNA that contains the SOC-2/CRAC-1 sequences of SEQ ID NO:1, SEQ ID NO:3, and SEQ ID NO:5.

SEQ ID NO:24 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:23).

SEQ ID NO:25 is a partial nucleotide sequence of the human SOC-3/CRAC-2 cDNA.

SEQ ID NO:26 is the predicted amino acid sequence of the translation product of human SOC-3/CRAC-2 cDNA (SEQ ID NO:25).

SEQ ID NO:27 is the full nucleotide sequence of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:28 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:27).

SEQ ID NO:29 is the full nucleotide sequence of the human SOC-3/CRAC-2 cDNA.

SEQ ID NO:30 is the predicted amino acid sequence of the translation product of human SOC-3/CRAC-2 cDNA (SEQ ID NO:29).

SEQ ID NO:31 is the full nucleotide sequence of the human SOC-4/CRAC-3 cDNA.

SEQ ID NO:32 is the predicted amino acid sequence of the translation product of human SOC-4/CRAC-3 cDNA (SEQ ID NO:31).

Brief Description of the Drawings

Figure 1 is a schematic depicting the intron/exon organization of the chicken SOC-2/CRAC-1 genomic sequence, as well as the putative transmembrane (TM) domains, and the targeting constructs utilized in the knockout experiments.

Detailed Description of the Invention

One aspect of the invention involves the partial cloning of cDNAs encoding members of a novel family of calcium channel polypeptides, referred to herein as "SOC/CRAC" (designated "SOC" or "CRAC" or "ICRAC", for StoRe Operated Channels or Calcium Release Activated Channels, or CECH). Although not intending to be bound to any particular mechanism or theory, we believe that a SOC/CRAC family member is a transmembrane calcium channel that modulates Ca^{2+} flux "into" and "out of" a cell; in certain instances it may be activated upon depletion of Ca^{2+} from intracellular calcium stores, allowing Ca^{2+} influx into the cell.

The first three isolated SOC/CRAC members disclosed herein, define a new family of calcium channels which is distinct from previously described calcium channels, such as voltage gated calcium channels, ryanodine receptor/inositol-1,4,5-triphosphate receptor

channels, and Transient Receptor Potential (TRP) channels. The SOC/CRAC family of calcium channels exhibits high selectivity (with a P_{Ca}/P_{Na} ratio near 1000), a unitary conductance below the detection level of the patch clamp method (the conductance estimated at approximately 0.2 picosiemens), and are subject to inhibition by high intracellular calcium levels. Although not intending to be bound to any particular mechanism or theory, we believe that SOC/CRAC calcium channels are responsible for the majority of, for example, calcium entry which occurs when intracellular calcium stores are depleted, and that SOC/CRAC currents are important for initiating various types of calcium-dependent processes. Thus, we believe that SOC/CRAC calcium channels play an important role in cellular calcium homeostasis by, e.g., modulating the supply of calcium to refill intracellular stores when depleted.

The isolated full-length sequence of a representative, first member of the SOC/CRAC family, human SOC/CRAC nucleic acid (cDNA), SOC-2/CRAC-1, is represented as the nucleic acid of SEQ ID NO:27. This nucleic acid sequence codes for the SOC-2/CRAC-1 polypeptide with the predicted amino acid sequence disclosed herein as SEQ ID NO:28. A homologous mouse cDNA sequence (>90% identity to the human at the nucleotide level) is represented as the nucleic acid of SEQ ID NO:7, and codes for a unique fragment of a mouse SOC-2/CRAC-1 polypeptide having the predicted, partial amino acid sequence represented as SEQ ID NO:8. Analysis of the SOC-2/CRAC-1 partial sequence by comparison to nucleic acid and protein databases show that SOC-2/CRAC-1 shares a limited homology to mouse MLSN-1 (SOC-1, SEQ ID NOs: 9 and 10). Limited homology is also shared between SOC-2/CRAC-1 and three *C. Elegans* polypeptides (SEQ ID NOs: 13, 14, and 15). We further believe that SOC-2/CRAC-1 plays a role in the regulation of cellular Ca^{2+} fluxing and, in particular, lymphocyte Ca^{2+} fluxing.

A second member of the human SOC/CRAC family of calcium channels, SOC-3/CRAC-2, is represented as the nucleic acid of SEQ ID NO:29, and codes for the human SOC-3/CRAC-2 polypeptide having the predicted amino acid sequence represented as SEQ ID NO:30 (this molecule may also be referred to as CECH2). SOC-3/CRAC-2 is predominantly expressed in human hematopoietic cells (including peripheral blood lymphocytes, liver, bone marrow, spleen, thymus, lymph nodes, heart, and kidney. Expression can also be detected (at lesser levels) in brain, skeletal muscle colon, small intestine, placenta, lung, and cells (cell lines) such as HL-60, HeLa, K562, MOLT-4, SW-480, A459, and G361.

A third member of the human SOC/CRAC family of calcium channels, SOC-4/CRAC-3, is represented as the nucleic acid of SEQ ID NO:31, and codes for the human SOC-4/CRAC-3 polypeptide having the predicted amino acid sequence represented as SEQ ID NO:32 (this molecule may also be referred to as CECH6). It specifically expressed in the prostate gland/cells.

As used herein, a SOC/CRAC calcium channel nucleic acid (also referred to herein as a "SOC/CRAC nucleic acid" refers to a nucleic acid molecule which: (1) hybridizes under stringent conditions to one or more of the nucleic acids having the sequences of SEQ. ID NOS. 7, 27, 29, and/or 31 (sequences of the mouse and human SOC-2/CRAC-1, human SOC-3/CRAC-2, and human SOC-4/CRAC-3 nucleic acids), and (2) codes for a SOC-2/CRAC-1, a SOC-3/CRAC-2 or a SOC-4/CRAC-3 calcium channel polypeptide, respectively, or unique fragments of said SOC-2/CRAC-1, SOC-3/CRAC-2, or SOC-4/CRAC-3 polypeptide.

As used herein, a SOC/CRAC calcium channel polypeptide (also referred to herein as a "SOC/CRAC polypeptide") refers to a polypeptide that is coded for by a SOC-2/CRAC-1, a SOC-3/CRAC-2, and/or a SOC-4/CRAC-3 nucleic acid. Preferably, the above-identified SOC/CRAC polypeptides mediate transport of calcium into and out of a cell.

SOC/CRAC polypeptides also are useful as immunogenic molecules for the generation of binding polypeptides (e.g., antibodies) which bind selectively to SOC/CRAC (e.g., SOC-2/CRAC-1, SOC-3/CRAC-2, and/or SOC-4/CRAC-3) polypeptides. Such antibodies can be used in diagnostic assays to identify and/or quantify the presence of a SOC/CRAC polypeptide in a sample, such as a biological fluid or biopsy sample. SOC/CRAC polypeptides further embrace functionally equivalent fragments, variants, and analogs of the preferred SOC/CRAC polypeptides, provided that the fragments, variants, and analogs also are useful in mediating calcium transport into and out of intracellular calcium stores.

As used herein, "SOC/CRAC calcium channel activity" refers to Ca^{2+} transport ("Ca²⁺ fluxing") across the plasma membrane that is mediated by a SOC/CRAC calcium channel polypeptide. The SOC/CRAC calcium channel polypeptide typically has one or more of the following properties: high selectivity, a unitary conductance below the detection level of the patch clamp method, and are subject to inhibition by high intracellular calcium levels. Such activity can be easily detected using standard methodology well known in the art. See, e.g., the Examples and Neher, E., "Ion channels for communication between and within cells",

Science, 1992; 256:498-502; and Hoth, M., and Penner, R., "Depletion of intracellular calcium stores activates a calcium current in mast cells", Nature, 1992; 355 (6358):353-6.

According to one aspect of the invention, isolated nucleic acid molecules which code for one or more member(s) of the SOC/CRAC family of calcium channel polypeptides are provided. The isolated nucleic acid molecules are selected from the following groups:

(a) nucleic acid molecules which hybridize under stringent conditions to one or more nucleic acid molecules selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, and which code for a SOC/CRAC polypeptide;

(b) deletions, additions and substitutions of (a) which code for a respective SOC/CRAC polypeptide;

(c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) in codon sequence due to the degeneracy of the genetic code, and

(d) complements of (a), (b) or (c).

In certain embodiments, the isolated nucleic acid molecule comprises one or more of nucleotides 1-1212 of SEQ ID NO:1; nucleotides 1-739 of SEQ ID NO:3; nucleotides 1-1579 of SEQ ID NO:5; nucleotides 1-5117 of SEQ ID NO:23; the mouse homolog for SOC-2/CRAC-1 corresponding to SEQ ID NO:7; nucleotides 1-2180 of SEQ ID NO:25; nucleotides 382-5976 of SEQ ID NO:27; nucleotides 73-3714 of SEQ ID NO:29; and nucleotides 23-3434 of SEQ ID NO:31. In yet other embodiments, the isolated nucleic acid molecule comprises a molecule which encodes a polypeptide having one or more sequences selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32.

According to yet another aspect of the invention, an isolated nucleic acid molecule is provided which is selected from the group consisting of:

(a) a unique fragment of a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, (of sufficient length to represent a sequence unique within the human genome); and (b) complements of (a), provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to a sequence in the prior art as represented by the sequence group consisting of: (1) sequences having the SEQ ID NOs or GenBank accession numbers of Table I, (2) complements of (1), and (3) fragments of (1) and (2).

In some embodiments, the sequence of contiguous nucleotides is selected from the group consisting of (1) at least two contiguous nucleotides nonidentical to the sequence group, (2) at least three contiguous nucleotides nonidentical to the sequence group, (3) at least four contiguous nucleotides nonidentical to the sequence group, (4) at least five contiguous nucleotides nonidentical to the sequence group, (5) at least six contiguous nucleotides nonidentical to the sequence group, (6) at least seven contiguous nucleotides nonidentical to the sequence group.

In other embodiments, the unique fragment has a size selected from the group consisting of at least: 8 nucleotides, 10 nucleotides, 12 nucleotides, 14 nucleotides, 16 nucleotides, 18 nucleotides, 20, nucleotides, 22 nucleotides, 24 nucleotides, 26 nucleotides, 28 nucleotides, 30 nucleotides, 40 nucleotides, 50 nucleotides, 75 nucleotides, 100 nucleotides, 200 nucleotides, 1000 nucleotides and every integer length therebetween.

According to another aspect of the invention, expression vectors and host cells containing (e.g., transformed or transfected with) expression vectors comprising the nucleic acid molecules disclosed herein operably linked to a promoter are provided. In certain preferred embodiments, the host cells are eukaryotic cells.

The isolated nucleic acid molecules disclosed herein have various utilities, including their use as probes and primers to identify additional members of the SOC/CRAC family of calcium channels, as diagnostic reagents for identifying the presence of SOC/CRAC polypeptides in biological or other samples, and as agents for generating SOC/CRAC binding polypeptides (e.g., antibodies) that can be used as reagents in diagnostic and therapeutic assays to identify the presence, absence, and/or amounts of a SOC/CRAC nucleic acid or polypeptide in a biological or other sample.

As used herein with respect to nucleic acids, the term "isolated" means: (i) amplified *in vitro* by, for example, polymerase chain reaction (PCR); (ii) recombinantly produced by cloning; (iii) purified, as by cleavage and gel separation; or (iv) synthesized by, for example, chemical synthesis. An isolated nucleic acid is one which is readily manipulatable by recombinant DNA techniques well known in the art. Thus, a nucleotide sequence contained in a vector in which 5' and 3' restriction sites are known or for which polymerase chain reaction (PCR) primer sequences have been disclosed is considered isolated but a nucleic acid sequence existing in its native state in its natural host is not. An isolated nucleic acid may be substantially purified, but need not be. For example, a nucleic acid that is isolated within a cloning or expression vector is not pure in that it may comprise only a tiny percentage of the

material in the cell in which it resides. Such a nucleic acid is isolated, however, as the term is used herein because it is readily manipulatable by standard techniques known to those of ordinary skill in the art.

As used herein with respect to polypeptides (discussed below), the term "isolated" means separated from its native environment in sufficiently pure form so that it can be manipulated or used for any one of the purposes of the invention. Thus, isolated means sufficiently pure to be used (i) to raise and/or isolate antibodies, (ii) as a reagent in an assay, or (iii) for sequencing, etc.

Homologs and alleles of the SOC/CRAC nucleic acids of the invention can be identified by conventional techniques. Thus, an aspect of the invention is those nucleic acid sequences which code for SOC/CRAC polypeptides and which hybridize to a nucleic acid molecule selected from a group consisting of the nucleic acid of SEQ ID NO:1, the nucleic acid of SEQ ID NO:3, the nucleic acid of SEQ ID NO:5, the nucleic acid of SEQ ID NO:7, the nucleic acid of SEQ ID NO:23, the nucleic acid of SEQ ID NO:25, the nucleic acid of SEQ ID NO:27, the nucleic acid of SEQ ID NO:29, and the nucleic acid of SEQ ID NO:31, under stringent conditions. The term "stringent conditions" as used herein refers to parameters with which the art is familiar. Nucleic acid hybridization parameters may be found in references which compile such methods, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. More specifically, stringent conditions, as used herein, refers, for example, to hybridization at 65°C in hybridization buffer (3.5 x SSC, 0.02% Ficoll, 0.02% polyvinyl pyrrolidone, 0.02% Bovine Serum Albumin, 2.5mM NaH₂PO₄(pH7), 0.5% SDS, 2mM EDTA). SSC is 0.15M sodium chloride/0.15M sodium citrate, pH7; SDS is sodium dodecyl sulphate; and EDTA is ethylenediaminetetracetic acid. After hybridization, the membrane upon which the DNA is transferred is washed at 2 x SSC at room temperature and then at 0.1 x SSC/0.1 x SDS at temperatures up to 68°C.

There are other conditions, reagents, and so forth which can be used, and would result in a similar degree of stringency. The skilled artisan will be familiar with such conditions, and thus they are not given here. It will be understood, however, that the skilled artisan will be able to manipulate the conditions in a manner to permit the clear identification of homologs and alleles of the SOC/CRAC nucleic acids of the invention. The skilled artisan also is familiar with the methodology for screening cells and libraries for expression of such

molecules which then are routinely isolated, followed by isolation of the pertinent nucleic acid molecule and sequencing.

In general homologs and alleles typically will share at least 40% nucleotide identity and/or at least 50% amino acid identity to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and/or SEQ ID NO:31, and SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and/or SEQ ID NO:32, respectively. In some instances sequences will share at least 50% nucleotide identity and/or at least 65% amino acid identity and in still other instances sequences will share at least 60% nucleotide identity and/or at least 75% amino acid identity. The homology can be calculated using various, publicly available software tools developed by NCBI (Bethesda, Maryland) that can be obtained through the internet (<ftp://ncbi.nlm.nih.gov/pub/>). Exemplary tools include the BLAST system available at <http://www.ncbi.nlm.nih.gov>. Pairwise and ClustalW alignments (BLOSUM30 matrix setting) as well as Kyte-Doolittle hydropathic analysis can be obtained using the MacVector sequence analysis software (Oxford Molecular Group). Watson-Crick complements of the foregoing nucleic acids also are embraced by the invention.

In screening for SOC/CRAC related genes, such as homologs and alleles of SOC-2/CRAC-1 and/or SOC-3/CRAC-2, a Southern blot may be performed using the foregoing conditions, together with a radioactive probe. After washing the membrane to which the DNA is finally transferred, the membrane can be placed against X-ray film or a phosphorimager plate to detect the radioactive signal.

Given that the expression of the SOC/CRAC gene is prominent in certain human tissues (e.g., SOC-2/CRAC-1: lymphoid tissue/heart, SOC-3/CRAC-2: kidney/colon, SOC-4/CRAC-3: prostate), and given the teachings herein of partial human SOC/CRAC cDNA clones, full-length and other mammalian sequences corresponding to the human SOC/CRAC partial nucleic acid sequences can be isolated from, for example, a cDNA library prepared from one or more of the tissues in which SOC-2/CRAC-1 expression is prominent, SOC-3/CRAC-2 is prominent, and/or SOC-4/CRAC-3 expression is prominent, using standard colony hybridization techniques.

The invention also includes degenerate nucleic acids which include alternative codons to those present in the native materials. For example, serine residues are encoded by the codons TCA, AGT, TCC, TCG, TCT and AGC. Each of the six codons is equivalent for the purposes of encoding a serine residue. Thus, it will be apparent to one of ordinary skill in the

art that any of the serine-encoding nucleotide triplets may be employed to direct the protein synthesis apparatus, *in vitro* or *in vivo*, to incorporate a serine residue into an elongating SOC/CRAC polypeptide. Similarly, nucleotide sequence triplets which encode other amino acid residues include, but are not limited to: CCA, CCC, CCG and CCT (proline codons); CGA, CGC, CGG, CGT, AGA and AGG (arginine codons); ACA, ACC, ACG and ACT (threonine codons); AAC and AAT (asparagine codons); and ATA, ATC and ATT (isoleucine codons). Other amino acid residues may be encoded similarly by multiple nucleotide sequences. Thus, the invention embraces degenerate nucleic acids that differ from the biologically isolated nucleic acids in codon sequence due to the degeneracy of the genetic code.

The invention also provides isolated unique fragments of an isolated nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31. A unique fragment is one that is a 'signature' for the larger nucleic acid. For example, the unique fragment is long enough to assure that its precise sequence is not found in molecules within the human genome outside of the SOC/CRAC nucleic acids defined above (and human alleles). Those of ordinary skill in the art may apply no more than routine procedures to determine if a fragment is unique within the human genome.

Unique fragments, however, exclude fragments completely composed of the nucleotide sequences of any of GenBank accession numbers and SEQ ID NOs listed in Table I (SEQ ID NO:9, AB001535, AI226731, H18835, AA419592, AA261842, AA419407, AI098310, AA592910, D86107, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, AC005538, AA654650, AA370110, AA313170, AA493512, AI670079, AI671853, AC005538, AA654650, AA370110, AA313170, AA493512, AI670079, AI671853), or other previously published sequences as of the filing date of this application.

A fragment which is completely composed of the sequence described in the foregoing GenBank deposits and SEQ ID NO:9, is one which does not include any of the nucleotides unique to the sequences of the invention. Thus, a unique fragment must contain a nucleotide sequence other than the exact sequence of those in GenBank or fragments thereof. The difference may be an addition, deletion or substitution with respect to the GenBank sequence or it may be a sequence wholly separate from the GenBank sequence.

Unique fragments can be used as probes in Southern and Northern blot assays to identify such nucleic acids, or can be used in amplification assays such as those employing PCR. As known to those skilled in the art, large probes such as 200, 250, 300 or more nucleotides are preferred for certain uses such as Southern and Northern blots, while smaller fragments will be preferred for uses such as PCR. Unique fragments also can be used to produce fusion proteins for generating antibodies or determining binding of the polypeptide fragments, as demonstrated in the Examples, or for generating immunoassay components. Likewise, unique fragments can be employed to produce nonfused fragments of the SOC/CRAC polypeptides, useful, for example, in the preparation of antibodies, immunoassays or therapeutic applications. Unique fragments further can be used as antisense molecules to inhibit the expression of SOC/CRAC nucleic acids and polypeptides, respectively.

As will be recognized by those skilled in the art, the size of the unique fragment will depend upon its conservancy in the genetic code. Thus, some regions of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, and complements thereof, will require longer segments to be unique while others will require only short segments, typically between 12 and 32 nucleotides long (e.g. 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 and 32 bases) or more, up to the entire length of the disclosed sequence. As mentioned above, this disclosure intends to embrace each and every fragment of each sequence, beginning at the first nucleotide, the second nucleotide and so on, up to 8 nucleotides short of the end, and ending anywhere from nucleotide number 8, 9, 10 and so on for each sequence, up to the very last nucleotide, (provided the sequence is unique as described above). Virtually any segment of the region of SEQ ID NO:1 beginning at nucleotide 1 and ending at nucleotide 1212, or SEQ ID NO:3 beginning at nucleotide 1 and ending at nucleotide 739, or SEQ ID NO:5 beginning at nucleotide 1 and ending at nucleotide 1579, or SEQ ID NO:7 beginning at nucleotide 1 and ending at nucleotide 3532, or SEQ ID NO:23 beginning at nucleotide 1 and ending at nucleotide 5117, SEQ ID NO:25 beginning at nucleotide 1 and ending at nucleotide 2180, SEQ ID NO:27 beginning at nucleotide 1 and ending at nucleotide 7419, or SEQ ID NO:29 beginning at nucleotide 1 and ending at nucleotide 4061, or SEQ ID NO:31 beginning at nucleotide 1 and ending at nucleotide 4646, or complements thereof, that is 20 or more nucleotides in length will be unique. Those skilled in the art are well versed in methods for selecting such sequences, typically on the basis of the ability of the unique

fragment to selectively distinguish the sequence of interest from other sequences in the human genome of the fragment to those on known databases typically is all that is necessary, although *in vitro* confirmatory hybridization and sequencing analysis may be performed.

As mentioned above, the invention embraces antisense oligonucleotides that selectively bind to a nucleic acid molecule encoding a SOC/CRAC polypeptide, to decrease SOC/CRAC calcium channel activity. When using antisense preparations of the invention, slow intravenous administration is preferred.

As used herein, the term "antisense oligonucleotide" or "antisense" describes an oligonucleotide that is an oligoribonucleotide, oligodeoxyribonucleotide, modified oligoribonucleotide, or modified oligodeoxyribonucleotide which hybridizes under physiological conditions to DNA comprising a particular gene or to an mRNA transcript of that gene and, thereby, inhibits the transcription of that gene and/or the translation of that mRNA. The antisense molecules are designed so as to interfere with transcription or translation of a target gene upon hybridization with the target gene or transcript. Those skilled in the art will recognize that the exact length of the antisense oligonucleotide and its degree of complementarity with its target will depend upon the specific target selected, including the sequence of the target and the particular bases which comprise that sequence. It is preferred that the antisense oligonucleotide be constructed and arranged so as to bind selectively with the target under physiological conditions, i.e., to hybridize substantially more to the target sequence than to any other sequence in the target cell under physiological conditions. Based upon SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, or upon allelic or homologous genomic and/or cDNA sequences, one of skill in the art can easily choose and synthesize any of a number of appropriate antisense molecules for use in accordance with the present invention. In order to be sufficiently selective and potent for inhibition, such antisense oligonucleotides should comprise at least 10 and, more preferably, at least 15 consecutive bases which are complementary to the target, although in certain cases modified oligonucleotides as short as 7 bases in length have been used successfully as antisense oligonucleotides (Wagner et al., *Nat. Med.* 1(11):1116-1118, 1995). Most preferably, the antisense oligonucleotides comprise a complementary sequence of 20-30 bases. Although oligonucleotides may be chosen which are antisense to any region of the gene or mRNA transcripts, in preferred embodiments the antisense oligonucleotides correspond to N-terminal or 5' upstream sites such as translation initiation, transcription initiation or promoter sites. In

addition, 3'-untranslated regions may be targeted by antisense oligonucleotides. Targeting to mRNA splicing sites has also been used in the art but may be less preferred if alternative mRNA splicing occurs. In addition, the antisense is targeted, preferably, to sites in which mRNA secondary structure is not expected (see, e.g., Sainio et al., *Cell Mol. Neurobiol.* 14(5):439-457, 1994) and at which proteins are not expected to bind. Finally, although, SEQ ID No:1 discloses a cDNA sequence, one of ordinary skill in the art may easily derive the genomic DNA corresponding to this sequence. Thus, the present invention also provides for antisense oligonucleotides which are complementary to the genomic DNA corresponding to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31. Similarly, antisense to allelic or homologous SOC/CRAC cDNAs and genomic DNAs are enabled without undue experimentation.

In one set of embodiments, the antisense oligonucleotides of the invention may be composed of "natural" deoxyribonucleotides, ribonucleotides, or any combination thereof. That is, the 5' end of one native nucleotide and the 3' end of another native nucleotide may be covalently linked, as in natural systems, via a phosphodiester internucleoside linkage. These oligonucleotides may be prepared by art recognized methods which may be carried out manually or by an automated synthesizer. They also may be produced recombinantly by vectors.

In preferred embodiments, however, the antisense oligonucleotides of the invention also may include "modified" oligonucleotides. That is, the oligonucleotides may be modified in a number of ways which do not prevent them from hybridizing to their target but which enhance their stability or targeting or which otherwise enhance their therapeutic effectiveness.

The term "modified oligonucleotide" as used herein describes an oligonucleotide in which (1) at least two of its nucleotides are covalently linked via a synthetic internucleoside linkage (i.e., a linkage other than a phosphodiester linkage between the 5' end of one nucleotide and the 3' end of another nucleotide) and/or (2) a chemical group not normally associated with nucleic acids has been covalently attached to the oligonucleotide. Preferred synthetic internucleoside linkages are phosphorothioates, alkylphosphonates, phosphorodithioates, phosphate esters, alkylphosphonothioates, phosphoramidates, carbamates, carbonates, phosphate triesters, acetamides, carboxymethyl esters and peptides.

The term "modified oligonucleotide" also encompasses oligonucleotides with a covalently modified base and/or sugar. For example, modified oligonucleotides include

-20-

oligonucleotides having backbone sugars which are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 3' position and other than a phosphate group at the 5' position. Thus modified oligonucleotides may include a 2'-O-alkylated ribose group. In addition, modified oligonucleotides may include sugars such as arabinose instead of ribose. The present invention, thus, contemplates pharmaceutical preparations containing modified antisense molecules that are complementary to and hybridizable with, under physiological conditions, nucleic acids encoding SOC/CRAC polypeptides, together with pharmaceutically acceptable carriers. Antisense oligonucleotides may be administered as part of a pharmaceutical composition. Such a pharmaceutical composition may include the antisense oligonucleotides in combination with any standard physiologically and/or pharmaceutically acceptable carriers which are known in the art. The compositions should be sterile and contain a therapeutically effective amount of the antisense oligonucleotides in a unit of weight or volume suitable for administration to a patient. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients. The term "physiologically acceptable" refers to a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism. The characteristics of the carrier will depend on the route of administration. Physiologically and pharmaceutically acceptable carriers include diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials which are well known in the art.

The invention also involves expression vectors coding for SOC/CRAC proteins and fragments and variants thereof and host cells containing those expression vectors. Virtually any cells, prokaryotic or eukaryotic, which can be transformed with heterologous DNA or RNA and which can be grown or maintained in culture, may be used in the practice of the invention. Examples include bacterial cells such as *E.coli* and eukaryotic cells such as mouse, hamster, pig, goat, primate, yeast, xenopous, etc. They may be of a wide variety of tissue types, including mast cells, fibroblasts, oocytes and lymphocytes, and they may be primary cells or cell lines. Specific examples include CHO cells and COS cells. Cell-free transcription systems also may be used in lieu of cells.

As used herein, a "vector" may be any of a number of nucleic acids into which a desired sequence may be inserted by restriction and ligation for transport between different genetic environments or for expression in a host cell. Vectors are typically composed of DNA although RNA vectors are also available. Vectors include, but are not limited to,

plasmids, phagemids and virus genomes. A cloning vector is one which is able to replicate in a host cell, and which is further characterized by one or more endonuclease restriction sites at which the vector may be cut in a determinable fashion and into which a desired DNA sequence may be ligated such that the new recombinant vector retains its ability to replicate in the host cell. In the case of plasmids, replication of the desired sequence may occur many times as the plasmid increases in copy number within the host bacterium or just a single time per host before the host reproduces by mitosis. In the case of phage, replication may occur actively during a lytic phase or passively during a lysogenic phase. An expression vector is one into which a desired DNA sequence may be inserted by restriction and ligation such that it is operably joined to regulatory sequences and may be expressed as an RNA transcript. Vectors may further contain one or more marker sequences suitable for use in the identification of cells which have or have not been transformed or transfected with the vector. Markers include, for example, genes encoding proteins which increase or decrease either resistance or sensitivity to antibiotics or other compounds, genes which encode enzymes whose activities are detectable by standard assays known in the art (e.g., β -galactosidase or alkaline phosphatase), and genes which visibly affect the phenotype of transformed or transfected cells, hosts, colonies or plaques (e.g., green fluorescent protein). Preferred vectors are those capable of autonomous replication and expression of the structural gene products present in the DNA segments to which they are operably joined.

As used herein, a coding sequence and regulatory sequences are said to be "operably" joined when they are covalently linked in such a way as to place the expression or transcription of the coding sequence under the influence or control of the regulatory sequences. If it is desired that the coding sequences be translated into a functional protein, two DNA sequences are said to be operably joined if induction of a promoter in the 5' regulatory sequences results in the transcription of the coding sequence and if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter region to direct the transcription of the coding sequences, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. Thus, a promoter region would be operably joined to a coding sequence if the promoter region were capable of effecting transcription of that DNA sequence such that the resulting transcript might be translated into the desired protein or polypeptide.

The precise nature of the regulatory sequences needed for gene expression may vary between species or cell types, but shall in general include, as necessary, 5' non-transcribed

and 5' non-translated sequences involved with the initiation of transcription and translation respectively, such as a TATA box, capping sequence, CAAT sequence, and the like. Especially, such 5' non-transcribed regulatory sequences will include a promoter region which includes a promoter sequence for transcriptional control of the operably joined gene. Regulatory sequences may also include enhancer sequences or upstream activator sequences as desired. The vectors of the invention may optionally include 5' leader or signal sequences. The choice and design of an appropriate vector is within the ability and discretion of one of ordinary skill in the art.

According to yet another aspect of the invention, isolated SOC/CRAC polypeptides are provided. Preferably, the isolated SOC/CRAC polypeptides are encoded by the isolated SOC/CRAC nucleic acid molecules disclosed herein. More preferably, the isolated SOC/CRAC polypeptides of the invention are encoded by the nucleic acid molecules having SEQ ID Nos. 1, 3, 5, 7, 23, 25, 27, 29, and 31. In yet other embodiments, the isolated SOC/CRAC polypeptides of the invention have an amino acid sequence selected from the group consisting of SEQ ID Nos. 2, 4, 6, 8, 24, 26, 28, 30 and 32. Preferably, the isolated SOC/CRAC polypeptides are of sufficient length to represent a sequence unique within the human genome. Thus, the preferred embodiments include a sequence of contiguous amino acids which is not identical to a prior art sequence as represented by the sequence group consisting of the contiguous amino acids identified in Table II (SEQ ID NO:10, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19 and GenBank Acc. Nos. AB001535, AA592910, D86107, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, NP003298, CAB00861, NP002411, CAA92726, CAB05572).

In certain embodiments, the isolated SOC/CRAC polypeptides are immunogenic and can be used to generate binding polypeptides (e.g., antibodies) for use in diagnostic and therapeutic applications. Such binding polypeptides also are useful for detecting the presence, absence, and/or amounts of a SOC/CRAC nucleic acid or polypeptide in a sample such as a biological fluid or biopsy sample. Preferably, the SOC/CRAC polypeptides that are useful for generating binding polypeptides are unique polypeptides and, therefore, binding of the antibody to a SOC/CRAC polypeptide in a sample is selective for the SOC/CRAC polypeptide.

Expression vectors containing all the necessary elements for expression are commercially available and known to those skilled in the art. See, e.g., Sambrook et al.,

Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989. Cells are genetically engineered by the introduction into the cells of heterologous DNA (RNA) encoding a SOC/CRAC polypeptide or fragment or variant thereof. The heterologous DNA (RNA) is placed under operable control of transcriptional elements to permit the expression of the heterologous DNA in the host cell.

Preferred systems for mRNA expression in mammalian cells are those such as pRc/CMV (available from Invitrogen, Carlsbad, CA) that contain a selectable marker such as a gene that confers G418 resistance (which facilitates the selection of stably transfected cell lines) and the human cytomegalovirus (CMV) enhancer-promoter sequences. Additionally, suitable for expression in primate or canine cell lines is the pCEP4 vector (Invitrogen, Carlsbad, CA), which contains an Epstein Barr virus (EBV) origin of replication, facilitating the maintenance of plasmid as a multicopy extrachromosomal element. Another expression vector is the pEF-BOS plasmid containing the promoter of polypeptide Elongation Factor 1 α , which stimulates efficiently transcription *in vitro*. The plasmid is described by Mishizuma and Nagata (*Nuc. Acids Res.* 18:5322, 1990), and its use in transfection experiments is disclosed by, for example, Demoulin (*Mol. Cell. Biol.* 16:4710-4716, 1996). Still another preferred expression vector is an adenovirus, described by Stratford-Perricaudet, which is defective for E1 and E3 proteins (*J. Clin. Invest.* 90:626-630, 1992). The use of the adenovirus as an Adeno.P1A recombinant is disclosed by Warnier et al., in intradermal injection in mice for immunization against P1A (*Int. J. Cancer*, 67:303-310, 1996).

The invention also embraces so-called expression kits, which allow the artisan to prepare a desired expression vector or vectors. Such expression kits include at least separate portions of each of the previously discussed coding sequences. Other components may be added, as desired, as long as the previously mentioned sequences, which are required, are included.

It will also be recognized that the invention embraces the use of the above described, SOC/CRAC cDNA sequence containing expression vectors, to transfect host cells and cell lines, by these prokaryotic (e.g., *E. coli*), or eukaryotic (e.g., CHO cells, COS cells, yeast expression systems and recombinant baculovirus expression in insect cells). Especially useful are mammalian cells such as mouse, hamster, pig, goat, primate, etc. They may be of a wide variety of tissue types, and include primary cells and cell lines. Specific examples include dendritic cells, U293 cells, peripheral blood leukocytes, bone marrow stem cells and embryonic stem cells. The invention also permits the construction of SOC/CRAC gene

“knock-outs” in cells and in animals, providing materials for studying certain aspects of SOC/CRAC calcium channel activity.

The invention also provides isolated polypeptides (including whole proteins and partial proteins), encoded by the foregoing SOC/CRAC nucleic acids, and include the polypeptides of SEQ ID NO:2, 4, 6, 8, 24, 26, 28, 30, 32, and unique fragments thereof. Such polypeptides are useful, for example, to regulate calcium transport-mediated cell growth, differentiation and proliferation, to generate antibodies, as components of immunoassays, etc. Polypeptides can be isolated from biological samples including tissue or cell homogenates, and can also be expressed recombinantly in a variety of prokaryotic and eukaryotic expression systems by constructing an expression vector appropriate to the expression system, introducing the expression vector into the expression system, and isolating the recombinantly expressed protein. Short polypeptides, including antigenic peptides (such as are presented by MHC molecules on the surface of a cell for immune recognition) also can be synthesized chemically using well-established methods of peptide synthesis.

A unique fragment of a SOC/CRAC polypeptide, in general, has the features and characteristics of unique fragments as discussed above in connection with nucleic acids. As will be recognized by those skilled in the art, the size of the unique fragment will depend upon factors such as whether the fragment constitutes a portion of a conserved protein domain. Thus, some regions of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and/or SEQ ID NO:32, will require longer segments to be unique while others will require only short segments, typically between 5 and 12 amino acids (e.g. 5, 6, 7, 8, 9, 10, 11 and 12 amino acids long or more, including each integer up to the full length, >1,000 amino acids long). Virtually any segment of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and/or SEQ ID NO:32, excluding the ones that share identity with it (the polypeptides identified in Table II - SEQ ID NO:10, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, and GenBank Acc. Nos. AB001535, AA592910, D86107, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, NP003298, CAB00861, NP002411, CAA92726, CAB05572) that is 9 or more amino acids in length will be unique.

Unique fragments of a polypeptide preferably are those fragments which retain a distinct functional capability of the polypeptide. Functional capabilities which can be retained in a unique fragment of a polypeptide include Ca^{2+} fluxing, high selectivity, a unitary

conductance below the detection level of the patch clamp method, and/or and are subject to inhibition by high intracellular calcium levels.

One important aspect of a unique fragment is its ability to act as a signature for identifying the polypeptide. Optionally, another aspect of a unique fragment is its ability to provide an immune response in an animal. Those skilled in the art are well versed in methods for selecting unique amino acid sequences, typically on the basis of the ability of the unique fragment to selectively distinguish the sequence of interest from non-family members. A comparison of the sequence of the fragment to those on known databases typically is all that is necessary.

The invention embraces variants of the SOC/CRAC polypeptides described above. As used herein, a "variant" of a SOC/CRAC polypeptide is a polypeptide which contains one or more modifications to the primary amino acid sequence of a SOC/CRAC polypeptide. Modifications which create a SOC/CRAC polypeptide variant are typically made to the nucleic acid which encodes the SOC/CRAC polypeptide, and can include deletions, point mutations, truncations, amino acid substitutions and addition of amino acids or non-amino acid moieties to: 1) reduce or eliminate a calcium channel activity of a SOC/CRAC polypeptide; 2) enhance a property of a SOC/CRAC polypeptide, such as protein stability in an expression system or the stability of protein-protein binding; 3) provide a novel activity or property to a SOC/CRAC polypeptide, such as addition of an antigenic epitope or addition of a detectable moiety; or 4) to provide equivalent or better binding to a SOC/CRAC polypeptide receptor or other molecule. Alternatively, modifications can be made directly to the polypeptide, such as by cleavage, addition of a linker molecule, addition of a detectable moiety, such as biotin, addition of a fatty acid, and the like. Modifications also embrace fusion proteins comprising all or part of the SOC/CRAC amino acid sequence. One of skill in the art will be familiar with methods for predicting the effect on protein conformation of a change in protein sequence, and can thus "design" a variant SOC/CRAC polypeptide according to known methods. One example of such a method is described by Dahiyat and Mayo in *Science* 278:82-87, 1997, whereby proteins can be designed *de novo*. The method can be applied to a known protein to vary only a portion of the polypeptide sequence. By applying the computational methods of Dahiyat and Mayo, specific variants of a SOC/CRAC calcium channel polypeptide can be proposed and tested to determine whether the variant retains a desired conformation.

5 Variants can include SOC/CRAC polypeptides which are modified specifically to alter a feature of the polypeptide unrelated to its physiological activity. For example, cysteine residues can be substituted or deleted to prevent unwanted disulfide linkages. Similarly, certain amino acids can be changed to enhance expression of a SOC/CRAC polypeptide by eliminating proteolysis by proteases in an expression system (e.g., dibasic amino acid residues in yeast expression systems in which KEX2 protease activity is present).

10 Mutations of a nucleic acid which encodes a SOC/CRAC polypeptide preferably preserve the amino acid reading frame of the coding sequence and, preferably, do not create regions in the nucleic acid which are likely to hybridize to form secondary structures, such as hairpins or loops, which can be deleterious to expression of the variant polypeptide.

15 Mutations can be made by selecting an amino acid substitution, or by random mutagenesis of a selected site in a nucleic acid which encodes the polypeptide. Variant polypeptides are then expressed and tested for one or more activities to determine which mutation provides a variant polypeptide with the desired properties. Further mutations can be made to variants (or to non-variant SOC/CRAC polypeptides) which are silent as to the amino acid sequence of the polypeptide, but which provide preferred codons for translation in a particular host. The preferred codons for translation of a nucleic acid in, e.g., *E. coli*, are well known to those of ordinary skill in the art. Still other mutations can be made to the noncoding sequences of a SOC/CRAC gene or cDNA clone to enhance expression of the polypeptide.

20 The skilled artisan will realize that conservative amino acid substitutions may be made in SOC/CRAC polypeptides to provide functionally equivalent variants of the foregoing polypeptides, i.e., the variants retain the functional capabilities of the SOC/CRAC polypeptides. As used herein, a "conservative amino acid substitution" refers to an amino acid substitution which does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Variants can be prepared according to methods for altering polypeptide sequence known to one of ordinary skill in the art such as are found in references which compile such methods, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. Exemplary functionally equivalent variants of the SOC/CRAC polypeptides include conservative amino acid substitutions of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and/or SEQ ID NO:32. Conservative substitutions of amino acids

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-27-

include substitutions made amongst amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q, N; and (g) E, D.

Thus functionally equivalent variants of SOC/CRAC polypeptides, i.e., variants of SOC/CRAC polypeptides which retain the function of the natural SOC/CRAC polypeptides, are contemplated by the invention. Conservative amino-acid substitutions in the amino acid sequence of SOC/CRAC polypeptides to produce functionally equivalent variants of SOC/CRAC polypeptides typically are made by alteration of a nucleic acid encoding SOC/CRAC polypeptides (e.g., SEQ ID NOs:1, 3, 5, 7, 23, 25, 27, 29, 31). Such substitutions can be made by a variety of methods known to one of ordinary skill in the art. For example, amino acid substitutions may be made by PCR-directed mutation, site-directed mutagenesis according to the method of Kunkel (Kunkel, *Proc. Nat. Acad. Sci. U.S.A.* 82: 488-492, 1985), or by chemical synthesis of a gene encoding a SOC/CRAC polypeptide. The activity of functionally equivalent fragments of SOC/CRAC polypeptides can be tested by cloning the gene encoding the altered SOC/CRAC polypeptide into a bacterial or mammalian expression vector, introducing the vector into an appropriate host cell, expressing the altered SOC/CRAC polypeptide, and testing for a functional capability of the SOC/CRAC polypeptides as disclosed herein (e.g., SOC/CRAC calcium channel activity).

The invention as described herein has a number of uses, some of which are described elsewhere herein. First, the invention permits isolation of SOC/CRAC polypeptides, including the isolation of the complete SOC/CRAC polypeptide. A variety of methodologies well-known to the skilled practitioner can be utilized to obtain isolated SOC/CRAC molecules. The polypeptide may be purified from cells which naturally produce the polypeptide by chromatographic means or immunological recognition. Alternatively, an expression vector may be introduced into cells to cause production of the polypeptide. In another method, mRNA transcripts may be microinjected or otherwise introduced into cells to cause production of the encoded polypeptide. Translation of SOC/CRAC mRNA in cell-free extracts such as the reticulocyte lysate system also may be used to produce SOC/CRAC polypeptides. Those skilled in the art also can readily follow known methods for isolating SOC/CRAC polypeptides. These include, but are not limited to, immunochromatography, HPLC, size-exclusion chromatography, ion-exchange chromatography and immune-affinity chromatography.

The invention also provides, in certain embodiments, "dominant negative" polypeptides derived from SOC/CRAC polypeptides. A dominant negative polypeptide is an

inactive variant of a protein, which, by interacting with the cellular machinery, displaces an active protein from its interaction with the cellular machinery or competes with the active protein, thereby reducing the effect of the active protein. For example, a dominant negative receptor which binds a ligand but does not transmit a signal in response to binding of the ligand can reduce the biological effect of expression of the ligand. Likewise, a dominant negative inactive SOC/CRAC calcium channel which interacts normally with the cell membrane but which does not mediate calcium transport can reduce calcium transport in a cell. Similarly, a dominant negative transcription factor which binds to a promoter site in the control region of a gene but does not increase gene transcription can reduce the effect of a normal transcription factor by occupying promoter binding sites without increasing transcription.

The end result of the expression of a dominant negative polypeptide in a cell is a reduction in function of active proteins. One of ordinary skill in the art can assess the potential for a dominant negative variant of a protein, and using standard mutagenesis techniques to create one or more dominant negative variant polypeptides. See, e.g., U.S. Patent No. 5,580,723 and Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press. The skilled artisan then can test the population of mutagenized polypeptides for diminution in a selected and/or for retention of such an activity. Other similar methods for creating and testing dominant negative variants of a protein will be apparent to one of ordinary skill in the art.

According to another aspect, the invention provides a method for isolating a SOC/CRAC molecule having SOC/CRAC calcium channel activity. The method involves contacting a binding molecule that is a SOC/CRAC nucleic acid or a SOC/CRAC binding polypeptide with a sample containing one or more SOC/CRAC molecules under conditions that allow such binding (see earlier discussion) to form a complex, detecting the presence of the complex, isolating the SOC/CRAC molecule from the complex, and determining whether the isolated SOC/CRAC molecule has SOC/CRAC calcium channel activity. Thus, the invention is useful for identifying and isolating full length complementary (cDNA) or genomic nucleic acids encoding SOC/CRAC polypeptides having SOC/CRAC calcium channel activity. Identification and isolation of such nucleic acids and polypeptides may be accomplished by hybridizing/binding, under appropriate conditions well known in the art, libraries and/or restriction enzyme-digested human nucleic acids, with a labeled SOC/CRAC molecular probe. As used herein, a "label" includes molecules that are incorporated into, for

example, a SOC/CRAC molecule (nucleic acid or peptide), that can be directly or indirectly detected. A wide variety of detectable labels are well known in the art that can be used, and include labels that provide direct detection (e.g., radioactivity, luminescence, optical or electron density, etc), or indirect detection (e.g., epitope tag such as the FLAG epitope, enzyme tag such as horseshoe peroxidase, etc.). The label may be bound to a SOC/CRAC binding partner, or incorporated into the structure of the binding partner.

A variety of methods may be used to detect the label, depending on the nature of the label and other assay components. For example, the label may be detected while bound to the solid substrate or subsequent to separation from the solid substrate. Labels may be directly detected through optical or electron density, radioactive emissions, nonradioactive energy transfers, etc. or indirectly detected with antibody conjugates, streptavidin-biotin conjugates, etc. Methods for detecting the labels are well known in the art. Once a library clone or hybridizing fragment is identified in the hybridization/binding reaction, it can be further isolated by employing standard isolation/cloning techniques known to those of skill in the art. See, generally, Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*, 2nd Edition, Cold Spring Harbor Laboratory Press. In addition, nucleic acid amplification techniques well known in the art, may also be used to locate splice variants of calcium channel (or calcium channel subunits) with SOC/CRAC calcium channel activity. Size and sequence determinations of the amplification products can reveal splice variants.

The foregoing isolated nucleic acids and polypeptides may then be compared to the nucleic acids and polypeptides of the present invention in order to identify homogeneity or divergence of the sequences, and be further characterized functionally to determine whether they belong to a family of molecules with SOC/CRAC calcium channel activity (for methodology see under the Examples section).

The isolation of the SOC/CRAC cDNA and/or partial sequences thereof also makes it possible for the artisan to diagnose a disorder characterized by an aberrant expression of SOC/CRAC. These methods involve determining expression of the SOC/CRAC gene, and/or SOC/CRAC polypeptides derived therefrom. In the former situation, such determinations can be carried out via any standard nucleic acid determination assay, including the polymerase chain reaction, or assaying with labeled hybridization probes as exemplified below. In the latter situation, such determination can be carried out via any standard immunological assay using, for example, antibodies which bind to the SOC/CRAC protein.

The invention also embraces isolated peptide binding agents which, for example, can be antibodies or fragments of antibodies ("binding polypeptides"), having the ability to selectively bind to SOC/CRAC polypeptides. Antibodies include polyclonal and monoclonal antibodies, prepared according to conventional methodology. In certain embodiments, the invention excludes binding agents (e.g., antibodies) that bind to the polypeptides encoded by the nucleic acids of SEQ ID NOs: 10, 12, 13, 14, 15, 17, and 19.

Significantly, as is well-known in the art, only a small portion of an antibody molecule, the paratope, is involved in the binding of the antibody to its epitope (see, in general, Clark, W.R. (1986) The Experimental Foundations of Modern Immunology Wiley & Sons, Inc., New York; Roitt, I. (1991) Essential Immunology, 7th Ed., Blackwell Scientific Publications, Oxford). The pFc' and Fc regions, for example, are effectors of the complement cascade but are not involved in antigen binding. An antibody from which the pFc' region has been enzymatically cleaved, or which has been produced without the pFc' region, designated an F(ab')₂ fragment, retains both of the antigen binding sites of an intact antibody. Similarly, an antibody from which the Fc region has been enzymatically cleaved, or which has been produced without the Fc region, designated an Fab fragment, retains one of the antigen binding sites of an intact antibody molecule. Proceeding further, Fab fragments consist of a covalently bound antibody light chain and a portion of the antibody heavy chain denoted Fd. The Fd fragments are the major determinant of antibody specificity (a single Fd fragment may be associated with up to ten different light chains without altering antibody specificity) and Fd fragments retain epitope-binding ability in isolation.

Within the antigen-binding portion of an antibody, as is well-known in the art, there are complementarity determining regions (CDRs), which directly interact with the epitope of the antigen, and framework regions (FRs), which maintain the tertiary structure of the paratope (see, in general, Clark, 1986; Roitt, 1991). In both the heavy chain Fd fragment and the light chain of IgG immunoglobulins, there are four framework regions (FR1 through FR4) separated respectively by three complementarity determining regions (CDR1 through CDR3). The CDRs, and in particular the CDR3 regions, and more particularly the heavy chain CDR3, are largely responsible for antibody specificity.

It is now well-established in the art that the non-CDR regions of a mammalian antibody may be replaced with similar regions of conspecific or heterospecific antibodies while retaining the epitopic specificity of the original antibody. This is most clearly manifested in the development and use of "humanized" antibodies in which non-human CDRs

are covalently joined to human FR and/or Fc/pFc' regions to produce a functional antibody. Thus, for example, PCT International Publication Number WO 92/04381 teaches the production and use of humanized murine RSV antibodies in which at least a portion of the murine FR regions have been replaced by FR regions of human origin. Such antibodies, including fragments of intact antibodies with antigen-binding ability, are often referred to as "chimeric" antibodies.

Thus, as will be apparent to one of ordinary skill in the art, the present invention also provides for F(ab')₂, Fab, Fv and Fd fragments; chimeric antibodies in which the Fc and/or FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric F(ab')₂ fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric Fab fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; and chimeric Fd fragment antibodies in which the FR and/or CDR1 and/or CDR2 regions have been replaced by homologous human or non-human sequences. The present invention also includes so-called single chain antibodies.

Thus, the invention involves binding polypeptides of numerous size and type that bind selectively to SOC/CRAC polypeptides, and complexes containing SOC/CRAC polypeptides. These binding polypeptides also may be derived also from sources other than antibody technology. For example, such polypeptide binding agents can be provided by degenerate peptide libraries which can be readily prepared in solution, in immobilized form, as bacterial flagella peptide display libraries or as phage display libraries. Combinatorial libraries also can be synthesized of peptides containing one or more amino acids. Libraries further can be synthesized of peptides and non-peptide synthetic moieties.

Phage display can be particularly effective in identifying binding peptides useful according to the invention. Briefly, one prepares a phage library (using e.g. m13, fd, or lambda phage), displaying inserts from 4 to about 80 amino acid residues using conventional procedures. The inserts may represent, for example, a completely degenerate or biased array. One then can select phage-bearing inserts which bind to the SOC/CRAC polypeptide or a complex containing a SOC/CRAC polypeptide. This process can be repeated through several cycles of reselection of phage that bind to the SOC/CRAC polypeptide or complex. Repeated rounds lead to enrichment of phage bearing particular sequences. DNA sequence analysis can be conducted to identify the sequences of the expressed polypeptides. The minimal linear

portion of the sequence that binds to the SOC/CRAC polypeptide or complex can be determined. One can repeat the procedure using a biased library containing inserts containing part or all of the minimal linear portion plus one or more additional degenerate residues upstream or downstream thereof. Yeast two-hybrid screening methods also may be used to identify polypeptides that bind to the SOC/CRAC polypeptides. Thus, the SOC/CRAC polypeptides of the invention, or a fragment thereof, or complexes of SOC/CRAC can be used to screen peptide libraries, including phage display libraries, to identify and select peptide binding polypeptides that selectively bind to the SOC/CRAC polypeptides of the invention. Such molecules can be used, as described, for screening assays, for purification protocols, for interfering directly with the functioning of SOC/CRAC and for other purposes that will be apparent to those of ordinary skill in the art.

A SOC/CRAC polypeptide, or a fragment thereof, also can be used to isolate naturally occurring, polypeptide binding partners which may associate with the SOC/CRAC polypeptide in the membrane of a cell. Isolation of binding partners may be performed according to well-known methods. For example, isolated SOC/CRAC polypeptides can be attached to a substrate, and then a solution suspected of containing an SOC/CRAC binding partner may be applied to the substrate. If the binding partner for SOC/CRAC polypeptides is present in the solution, then it will bind to the substrate-bound SOC/CRAC polypeptide. The binding partner then may be isolated. Other proteins which are binding partners for SOC/CRAC, may be isolated by similar methods without undue experimentation.

The invention also provides novel kits which could be used to measure the levels of the nucleic acids of the invention, expression products of the invention or anti-SOC/CRAC antibodies. In the case of nucleic acid detection, pairs of primers for amplifying SOC/CRAC nucleic acids can be included. The preferred kits would include controls such as known amounts of nucleic acid probes, SOC/CRAC epitopes (such as SOC/CRAC expression products) or anti-SOC/CRAC antibodies, as well as instructions or other printed material. In certain embodiments the printed material can characterize risk of developing a disorder that is characterized by aberrant SOC/CRAC polypeptide expression based upon the outcome of the assay. The reagents may be packaged in containers and/or coated on wells in predetermined amounts, and the kits may include standard materials such as labeled immunological reagents (such as labeled anti-IgG antibodies) and the like. One kit is a packaged polystyrene microtiter plate coated with a SOC/CRAC polypeptide and a container containing labeled anti-human IgG antibodies. A well of the plate is contacted with, for example, serum, washed

and then contacted with the anti-IgG antibody. The label is then detected. A kit embodying features of the present invention is comprised of the following major elements: packaging an agent of the invention, a control agent, and instructions. Packaging is a box-like structure for holding a vial (or number of vials) containing an agent of the invention, a vial (or number of vials) containing a control agent, and instructions. Individuals skilled in the art can readily modify packaging to suit individual needs.

Another aspect of the invention is a method for determining the level of SOC/CRAC expression in a subject. As used herein, a subject is a human, non-human primate, cow, horse, pig, sheep, goat, dog, cat or rodent. In all embodiments, human subjects are preferred. Expression is defined either as SOC/CRAC mRNA expression or SOC/CRAC polypeptide expression. Various methods can be used to measure expression. Preferred embodiments of the invention include PCR and Northern blotting for measuring mRNA expression, and monoclonal or polyclonal SOC/CRAC antisera as reagents to measure SOC/CRAC polypeptide expression. In certain embodiments, test samples such as biopsy samples, and biological fluids such as blood, are used as test samples. SOC/CRAC expression in a test sample of a subject is compared to SOC/CRAC expression in control sample to, e.g., assess the presence or absence or stage of a proliferative disorder (e.g., a lymphocyte proliferative disorder) in a subject.

SOC/CRAC polypeptides preferably are produced recombinantly, although such polypeptides may be isolated from biological extracts. Recombinantly produced SOC/CRAC polypeptides include chimeric proteins comprising a fusion of a SOC/CRAC protein with another polypeptide, e.g., a polypeptide capable of providing or enhancing protein-protein binding, sequence specific nucleic acid binding (such as GAL4), enhancing stability of the SOC/CRAC polypeptide under assay conditions, or providing a detectable moiety, such as green fluorescent protein. A polypeptide fused to a SOC/CRAC polypeptide or fragment may also provide means of readily detecting the fusion protein, e.g., by immunological recognition or by fluorescent labeling.

The invention is also useful in the generation of transgenic non-human animals. As used herein, "transgenic non-human animals" includes non-human animals having one or more exogenous nucleic acid molecules incorporated in germ line cells and/or somatic cells. Thus the transgenic animal include "knockout" animals having a homozygous or heterozygous gene disruption by homologous recombination, animals having episomal or chromosomally incorporated expression vectors, etc. Knockout animals can be prepared by

homologous recombination using embryonic stem cells as is well known in the art. The recombination may be facilitated using, for example, the cre/lox system or other recombinase systems known to one of ordinary skill in the art. In certain embodiments, the recombinase system itself is expressed conditionally, for example, in certain tissues or cell types, at certain embryonic or post-embryonic developmental stages, inducibly by the addition of a compound which increases or decreases expression, and the like. In general, the conditional expression vectors used in such systems use a variety of promoters which confer the desired gene expression pattern (e.g., temporal or spatial). Conditional promoters also can be operably linked to SOC/CRAC nucleic acid molecules to increase expression of SOC/CRAC in a regulated or conditional manner. *Trans*-acting negative regulators of SOC/CRAC calcium channel activity or expression also can be operably linked to a conditional promoter as described above. Such *trans*-acting regulators include antisense SOC/CRAC nucleic acids molecules, nucleic acid molecules which encode dominant negative SOC/CRAC molecules, ribozyme molecules specific for SOC/CRAC nucleic acids, and the like. The transgenic non-human animals are useful in experiments directed toward testing biochemical or physiological effects of diagnostics or therapeutics for conditions characterized by increased or decreased SOC/CRAC expression. Other uses will be apparent to one of ordinary skill in the art.

The invention further provides efficient methods of identifying agents or lead compounds for agents active at the level of a SOC/CRAC polypeptide (e.g., a SOC/CRAC polypeptide) or SOC/CRAC fragment dependent cellular function. In particular, such functions include interaction with other polypeptides or fragments thereof, and selective binding to certain molecules (e.g., agonists and antagonists). Generally, the screening methods involve assaying for compounds which interfere with SOC/CRAC calcium channel activity, although compounds which enhance SOC/CRAC calcium channel activity also can be assayed using the screening methods. Such methods are adaptable to automated, high throughput screening of compounds. The target therapeutic indications for pharmacological agents detected by the screening methods are limited only in that the target cellular function be subject to modulation by alteration of the formation of a complex comprising a SOC/CRAC polypeptide or fragment thereof and one or more SOC/CRAC binding targets. Target indications include cellular processes modulated by SOC/CRAC such as Ca^{2+} fluxing, and affected by SOC/CRAC ability to form complexes with other molecules and polypeptides as, for example, may be present in the cell membrane.

A wide variety of assays for pharmacological agents are provided, including, expression assays, labeled *in vitro* protein-protein binding assays, electrophoretic mobility shift assays, immunoassays, cell-based assays such as calcium transport assays, etc. For example, two-hybrid screens are used to rapidly examine the effect of transfected nucleic acids on the intracellular binding of SOC/CRAC or SOC/CRAC fragments to specific intracellular targets (e.g. a tyrosine kinase). The transfected nucleic acids can encode, for example, combinatorial peptide libraries or cDNA libraries. Convenient reagents for such assays, e.g., GAL4 fusion proteins, are known in the art. An exemplary cell-based assay involves transfecting a cell with a nucleic acid encoding a SOC/CRAC polypeptide fused to a GAL4 DNA binding domain and a nucleic acid encoding a reporter gene operably linked to a gene expression regulatory region, such as one or more GAL4 binding sites. Activation of reporter gene transcription occurs when the SOC/CRAC and reporter fusion polypeptides bind such as to enable transcription of the reporter gene. Agents which modulate a SOC/CRAC polypeptide mediated cell function are then detected through a change in the expression of reporter gene. Methods for determining changes in the expression of a reporter gene are known in the art.

In an expression system, for example, a SOC/CRAC polypeptide is attached to a membrane, the membrane preferably separating two fluid environments and being otherwise not permeable to Ca^{2+} . Such separation is preferred so that a change in Ca^{2+} concentration on either side of the membrane is mediated only through the attached SOC/CRAC polypeptide. Preferably, a SOC/CRAC polypeptide is expressed in an intact cell and is present on the cell-membrane (as in physiologic conditions). The cell expressing the SOC/CRAC polypeptide is preferably a eukaryotic cell, and the SOC/CRAC polypeptide is preferably recombinantly expressed, although cells naturally expressing a SOC/CRAC polypeptide may also be used. Synthetic membranes, however, containing SOC/CRAC polypeptides may also be used. See, e.g., K. Kiselyov, et al., Functional interaction between InsP3 receptors and store-operated Htrp3 channels, Nature 396, 478-82 (1998).

The cell expressing the SOC/CRAC polypeptide is incubated under conditions which, in the absence of the candidate agent, permit calcium flux into the cell and allow detection of a reference calcium concentration. For example, depletion of intracellular calcium stores with thapsigargin or other agents (Putney, J.W. Jr., in Capacitative Calcium Entry, R.G. Landes Co. and Chapman & Hall, 1997) would produce a given level of SOC/CRAC channel activation and a given reference calcium concentration. Detection of a decrease in the

foregoing activities (i.e., a decrease in the intracellular calcium concentration) relative to the reference calcium concentration indicates that the candidate agent is a lead compound for an agent to inhibit SOC/CRAC calcium channel activity. Preferred SOC/CRAC polypeptides include the polypeptides of claim 15.

5 SOC/CRAC fragments used in the methods, when not produced by a transfected nucleic acid are added to an assay mixture as an isolated polypeptide. SOC/CRAC polypeptides preferably are produced recombinantly, although such polypeptides may be isolated from biological extracts or chemically synthesized. Recombinantly produced SOC/CRAC polypeptides include chimeric proteins comprising a fusion of a SOC/CRAC
10 protein with another polypeptide, e.g., a polypeptide capable of providing or enhancing protein-protein binding, sequence specific nucleic acid binding (such as GAL4), enhancing stability of the SOC/CRAC polypeptide under assay conditions, or providing a detectable moiety, such as green fluorescent protein or Flag epitope.

The assay mixture is comprised of a SOC/CRAC polypeptide binding target
15 (candidate agent) capable of interacting with a SOC/CRAC polypeptide. While natural SOC/CRAC binding targets may be used, it is frequently preferred to use portions (e.g., peptides or nucleic acid fragments) or analogs (i.e., agents which mimic the SOC/CRAC binding properties of the natural binding target for purposes of the assay) of the SOC/CRAC binding target so long as the portion or analog provides binding affinity and avidity to the
20 SOC/CRAC polypeptide (or fragment thereof) measurable in the assay.

The assay mixture also comprises a candidate agent (binding target, e.g., agonist/antagonist). Typically, a plurality of assay mixtures are run in parallel with different agent concentrations to obtain a different response to the various concentrations. Typically, one of these concentrations serves as a negative control, i.e., at zero concentration of agent or
25 at a concentration of agent below the limits of assay detection. Candidate agents encompass numerous chemical classes, although typically they are organic compounds. Preferably, the candidate agents are small organic compounds, i.e., those having a molecular weight of more than 50 yet less than about 2500, preferably less than about 1000 and, more preferably, less than about 500. Candidate agents comprise functional chemical groups necessary for
30 structural interactions with polypeptides and/or nucleic acids, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups and more preferably at least three of the functional chemical groups. The candidate agents can comprise cyclic carbon or heterocyclic structure and/or aromatic or

polyaromatic structures substituted with one or more of the above-identified functional groups. Candidate agents also can be biomolecules such as peptides, saccharides, fatty acids, sterols, isoprenoids, purines, pyrimidines, derivatives or structural analogs of the above, or combinations thereof and the like. Where the agent is a nucleic acid, the agent typically is a DNA or RNA molecule, although modified nucleic acids as defined herein are also contemplated.

Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides, synthetic organic combinatorial libraries, phage display libraries of random peptides, and the like. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural and synthetically produced libraries and compounds can be readily modified through conventional chemical, physical, and biochemical means. Further, known agents may be subjected to directed or random chemical modifications such as acylation, alkylation, esterification, amidification, etc. to produce structural analogs of the agents. Non-SOC/CRAC calcium channel agonists and antagonists, for example, include agents such as dihydropyridines (DHPs), phenylalkylamines, omega conotoxin (omega.-CgTx) and pyrazonoylguanidines.

A variety of other reagents also can be included in the mixture. These include reagents such as salts, buffers, neutral proteins (e.g., albumin), detergents, etc. which may be used to facilitate optimal protein-protein, protein-nucleic acid, and/or protein/membrane component binding association. Such a reagent may also reduce non-specific or background interactions of the reaction components. Other reagents that improve the efficiency of the assay such as protease, inhibitors, nuclease inhibitors, antimicrobial agents, and the like may also be used.

The mixture of the foregoing assay materials is incubated under conditions whereby, but for the presence of the candidate agent, the SOC/CRAC polypeptide specifically binds the cellular binding target, a portion thereof or analog thereof. The order of addition of components, incubation temperature, time of incubation, and other perimeters of the assay may be readily determined. Such experimentation merely involves optimization of the assay parameters, not the fundamental composition of the assay. Incubation temperatures typically

are between 4°C and 40°C. Incubation times preferably are minimized to facilitate rapid, high throughput screening, and typically are between 0.1 and 10 hours.

After incubation, the presence or absence of specific binding between the SOC/CRAC polypeptide and one or more binding targets is detected by any convenient method available to the user. For cell free binding type assays, a separation step is often used to separate bound from unbound components. The separation step may be accomplished in a variety of ways. Conveniently, at least one of the components is immobilized on a solid substrate, from which the unbound components may be easily separated. The solid substrate can be made of a wide variety of materials and in a wide variety of shapes, e.g., microtiter plate, microbead, dipstick, resin particle, etc. The substrate preferably is chosen to maximum signal to noise ratios, primarily to minimize background binding, as well as for ease of separation and cost.

Separation may be effected for example, by removing a bead or dipstick from a reservoir, emptying or diluting a reservoir such as a microtiter plate well, rinsing a bead, particle, chromatographic column or filter with a wash solution or solvent. The separation step preferably includes multiple rinses or washes. For example, when the solid substrate is a microtiter plate, the wells may be washed several times with a washing solution, which typically includes those components of the incubation mixture that do not participate in specific bindings such as salts, buffer, detergent, non-specific protein, etc. Where the solid substrate is a magnetic bead, the beads may be washed one or more times with a washing solution and isolated using a magnet.

Detection may be effected in any convenient way for cell-based assays such as two- or three-hybrid screens. The transcript resulting from a reporter gene transcription assay of SOC/CRAC polypeptide interacting with a target molecule typically encodes a directly or indirectly detectable product, e.g., β -galactosidase activity, luciferase activity, and the like. For cell-free binding assays, one of the components usually comprises, or is coupled to, a detectable label. A wide variety of labels can be used, such as those that provide direct detection (e.g., radioactivity, luminescence, optical or electron density, etc.) or indirect detection (e.g., epitope tag such as the FLAG epitope, enzyme tag such as horseradish peroxidase, etc.). The label may be bound to a SOC/CRAC binding partner, or incorporated into the structure of the binding partner.

A variety of methods may be used to detect the label, depending on the nature of the label and other assay components. For example, the label may be detected while bound to the solid substrate or subsequent to separation from the solid substrate. Labels may be directly

detected through optical or electron density, radioactive emissions, nonradiative energy transfers, etc. or indirectly detected with antibody conjugates, strepavidin-biotin conjugates, etc. Methods for detecting the labels are well known in the art.

Of particular importance in any of the foregoing assays and binding studies is the use
5 of a specific sequence motif identified in the SOC-2/CRAC-1 polypeptide sequence as a kinase catalytic domain. According to the invention, amino acids 999-1180 of the SOC-2/CRAC-1 polypeptide (SEQ ID NO:24) (or a fragment thereof), show a localized homology with the catalytic domains of eukaryotic elongation factor-2 kinase (eEF-2 kinase, GenBank
10 Acc. no. U93850) and *Dictyostelium* myocin heavy chain kinase A (MHCK A, GenBank Acc. no. U16856), as disclosed in Ryazanov AG, et al., *Proc Natl Acad Sci U S A*, 1997, 94(10):4884-4889. Therefore, according to the invention, a method for identifying agents useful in the modulation of SOC/CRAC polypeptide kinase activity is provided. The method involves contacting a SOC/CRAC polypeptide with kinase activity, that includes, for example, amino acids 999-1180 of the SOC-2/CRAC-1 polypeptide (SEQ ID NO:24) with a
15 candidate agent suspected of modulating SOC/CRAC kinase activity, under conditions sufficient to allow the candidate agent to interact with the SOC/CRAC polypeptide and modulate its kinase activity; detecting a kinase activity associated with the SOC/CRAC polypeptide in the presence of the candidate agent; and comparing the kinase activity in the previous step with a control kinase activity of a SOC/CRAC polypeptide in the absence of the
20 candidate agent to determine whether the candidate agent modulates (increases or decreases) SOC/CRAC kinase activity. Other controls for kinase activity can also be performed at the same time, for example, by utilizing eEF-2 kinase and/or *Dictyostelium* MHC Kinase A, in a similar manner to the SOC/CRAC member. Methods for performing such kinase activity assays are well known in the art.

25 The invention thus provides SOC/CRAC-specific binding agents, methods of identifying and making such agents, and their use in diagnosis, therapy and pharmaceutical development. For example, SOC/CRAC-specific agents are useful in a variety of diagnostic and therapeutic applications, especially where disease or disease prognosis is associated with altered SOC/CRAC and SOC/CRAC calcium channel fluxing characteristics. Novel
30 SOC/CRAC-specific binding agents include SOC/CRAC-specific antibodies and other natural intracellular and extracellular binding agents identified with assays such as two hybrid screens, and non-natural intracellular and extracellular binding agents identified in screens of chemical libraries and the like.

In general, the specificity of SOC/CRAC binding to a specific molecule is determined by binding equilibrium constants. Targets which are capable of selectively binding a SOC/CRAC polypeptide preferably have binding equilibrium constants of at least about 10^7 M^{-1} , more preferably at least about 10^8 M^{-1} , and most preferably at least about 10^9 M^{-1} . The wide variety of cell based and cell free assays may be used to demonstrate SOC/CRAC-specific binding. Cell based assays include one, two and three hybrid screens, assays in which SOC/CRAC-mediated transcription is inhibited or increased, etc. Cell free assays include SOC/CRAC-protein binding assays, immunoassays, etc. Other assays useful for screening agents which bind SOC/CRAC polypeptides include fluorescence resonance energy transfer (FRET), and electrophoretic mobility shift analysis (EMSA).

Various techniques may be employed for introducing nucleic acids of the invention into cells, depending on whether the nucleic acids are introduced *in vitro* or *in vivo* in a host. Such techniques include transfection of nucleic acid- $CaPO_4$ precipitates, transfection of nucleic acids associated with DEAE, transfection with a retrovirus including the nucleic acid of interest, liposome mediated transfection, and the like. For certain uses, it is preferred to target the nucleic acid to particular cells. In such instances, a vehicle used for delivering a nucleic acid of the invention into a cell (e.g., a retrovirus, or other virus; a liposome) can have a targeting molecule attached thereto. For example, a molecule such as an antibody specific for a surface membrane protein on the target cell or a ligand for a receptor on the target cell can be bound to or incorporated within the nucleic acid delivery vehicle. For example, where liposomes are employed to deliver the nucleic acids of the invention, proteins which bind to a surface membrane protein associated with endocytosis may be incorporated into the liposome formulation for targeting and/or to facilitate uptake. Such proteins include capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half life, and the like. Polymeric delivery systems also have been used successfully to deliver nucleic acids into cells, as is known by those skilled in the art. Such systems even permit oral delivery of nucleic acids.

Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the anti-inflammatory agent, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer base systems such as poly(lactide-glycolide), copolyoxalates, polycaprolactones,

polyesteramides, polyorthoesters, polyhydroxybutyric acid, and polyanhydrides. Microcapsules of the foregoing polymers containing drugs are described in, for example, U.S. Patent 5,075,109. Delivery systems also include non-polymer systems that are: lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono- di- and tri-glycerides; hydrogel release systems; sylastic systems; peptide based systems; wax coatings; compressed tablets using conventional binders and excipients; partially fused implants; and the like. Specific examples include, but are not limited to: (a) erosional systems in which an agent of the invention is contained in a form within a matrix such as those described in U.S. Patent Nos. 4,452,775, 4,675,189, and 5,736,152, and (b) diffusional systems in which an active component permeates at a controlled rate from a polymer such as described in U.S. Patent Nos. 3,854,480, 5,133,974 and 5,407,686. In addition, pump-based hardware delivery systems can be used, some of which are adapted for implantation.

Use of a long-term sustained release implant may be particularly suitable for treatment of chronic conditions. Long-term release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 30 days, and preferably 60 days. Long-term sustained release implants are well-known to those of ordinary skill in the art and include some of the release systems described above.

The invention also contemplates gene therapy. The procedure for performing *ex vivo* gene therapy is outlined in U.S. Patent 5,399,346 and in exhibits submitted in the file history of that patent, all of which are publicly available documents. In general, it involves introduction *in vitro* of a functional copy of a gene into a cell(s) of a subject which contains a defective copy of the gene, and returning the genetically engineered cell(s) to the subject. The functional copy of the gene is under operable control of regulatory elements which permit expression of the gene in the genetically engineered cell(s). Numerous transfection and transduction techniques as well as appropriate expression vectors are well known to those of ordinary skill in the art, some of which are described in PCT application WO95/00654. *In vivo* gene therapy using vectors such as adenovirus, retroviruses, herpes virus, and targeted liposomes also is contemplated according to the invention. See, e.g., U.S. Patent Nos. 5,670,488, entitled "Adenovirus Vector for Gene Therapy", issued to Gregory et al., and 5,672,344, entitled "Viral-Mediated Gene Transfer System", issued to Kelley et al.

The invention will be more fully understood by reference to the following examples. These examples, however, are merely intended to illustrate the embodiments of the invention and are not to be construed to limit the scope of the invention.

Examples

5 As an initial approach to identifying SOC/CRAC channels, we considered publicly available data and hypothesized that the following characteristics are likely to be exhibited by SOC/CRAC calcium channels: i) SOC/CRAC calcium channels would be integral membrane proteins related (probably distantly) to one of the known calcium channel families (e.g. voltage gated, ligand gated, Trp), and therefore should have a pore region formed by a tetramer of 6-7 transmembrane (TM) regions; ii) high calcium selectivity was likely to come
10 at the price of complexity, and therefore these were likely to be large proteins; iii) the high calcium selectivity of this type of channel was likely to be useful and, therefore, highly conserved; and iv) these channels should be expressed in one or more types of lymphocytes, since ICRAC is best defined in those cell types. Since the full genome of the nematode *C. elegans* is nearing completion, and IP3-dependent calcium signals have recently been shown
15 to be required for one or more aspects of *C. elegans* development, we took the set of proteins encoded by this genome (at the time this search was initiated WORMPEP14 was the available predicted protein set) and began searching for proteins which fit the criteria above. This search began by proceeding in alphabetical order through WORMPEP14 and arbitrarily
20 excluding all proteins below approximately 1000 amino acids in size, followed by focusing on remaining proteins with clear TM spanning regions similar to those of other calcium channels. We stopped this screen on encountering a protein designated C05C12.3, a predicted protein of 1816 amino acids (SEQ ID NO:13). C05C12.3 was notable because its central pore region had some sequence similarity to but was clearly distinct from members of the Trp family of calcium channels, and the hydrophobicity plot of this region showed a
25 characteristically wide spacing between the fifth and sixth TM regions for the amino acid residues which are thought to line the channel pore region and mediate the calcium selectivity of the channels. In addition, it lacked any ankyrin repeats in the region amino-terminal to its pore region, further distinguishing it from other Trp family proteins.

30 We then used C05C12.3 for BLAST alignment screening of the rest of the *C. elegans* genome and also mammalian databases for homologous proteins, revealing two other *C. elegans* homologues (SEQ ID NO:14 and SEQ ID NO:15), and also a recently cloned mammalian protein named melastatin-1 (MLSN-1/SOC-1, SEQ ID NOs:9 and 10, and

GenBank Acc. No. AF071787). Using these sequences, we subsequently performed an exhaustive screening of publicly accessible EST databases in search of lymphocyte homologues, but were unsuccessful in detecting any homologous transcripts in any lymphocyte lines. Since MLSN-1 (SEQ ID NOs:9 and 10) was expressed exclusively in melanocytes and retina by Northern blot hybridization and by EST database searching, there was no evidence that this type of channel was expressed in the type of cell in which ICRAC-like currents were best defined. Subsequent BLAST searches picked up mouse EST sequence AI098310 (SEQ ID NO:22) from a monocyte cell line. The I.M.A.G.E. consortium clone containing the above-identified EST was then purchased from ATCC (clone ID. 1312756, Manassas, VA) and was further characterized. Using other portions of this sequence in EST searches, we subsequently picked up similar sequences in human B-cells (SEQ ID NOs:20 and 21), and other cell types as well (SEQ ID NOs: 11, 12, 16, 17, 18, and 19). Most of these sequences were subsequently identified to be part of the 3'-UTR or of the carboxy terminal region of the proteins, which are not readily identifiable as Trp channels, providing an explanation for the art's inability to detect any type of Trp related transcripts in lymphocytes. Partial sequences from the 5' and/or 3' ends of the above identified clones were then used to screen leukocyte and kidney cDNA libraries to extend the original sequences more toward the 5' and/or 3' ends.

In view of the foregoing, it was concluded that channels of this type were expressed in many types of lymphocytes, and therefore were members of a new family of SOC/CRAC calcium channels.

Experimental Procedures

Screening of the cDNA libraries

Leukocyte and kidney cDNA libraries from Life Technologies (Gaithersburg, MD) were screened using the Gene Trapper II methodology (Life Technologies) according to manufacturer's recommendation, using the inserts of I.M.A.G.E. clone ID nos. 1312756 and 1076485 from ATCC (Manassas, VA), under stringent hybridization conditions. Using standard methodology (*Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York), individual cDNA clones were subjected to 3-4 rounds of amplification and purification under the same hybridization conditions.

After excision from the vector and subcloning of inserts into the plasmid forms, several clones were sequenced by the Beth Israel Deaconess Medical Center's Automated

Sequencing Facility. Molecular biological techniques such as restriction enzyme treatment, subcloning, DNA extraction, bacterial culture and purification of DNA fragments were performed according to methods well known in the art. Computer analyses of protein and DNA sequences was done using "Assemblylign" (Oxford Molecular, Campbell, CA). Multiple
5 alignments of the SOC/CRAC family members were produced using the CLUSTAL facility of the MacVector program. Restriction endonucleases, expression vectors, and modifying enzymes were purchased from commercial sources (Gibco-BRL). Sequencing vectors for DNA were purchased from Stratagene (La Jolla, CA).

Once the first members of what appeared to be a novel family of calcium channel
10 receptors were identified and characterized, additional BLAST alignments were performed with the newly characterized nucleic acid sequences. An initial match was with genomic DNA fragment NH0332L11 (Genbank Acc. No. AC005538). Using this genomic sequence, promoters were designed and a number of cDNA libraries was surveyed by PCR. A prostate specific message was identified and characterized, leading to the isolation and
15 characterization of SOC-4/CRAC-3 (SEQ ID NOs: 31 and 32).

Functional Assays

Transient Expression of SOC/CRAC

In our initial transient expression experiments, we expressed or expect to express a SOC/CRAC molecule transiently in RBL-2H3 mast cells, Jurkat T cells, and A20
20 B-lymphocytes using both electroporation and vaccinia virus-driven expression, and measured the calcium influx produced by depletion of intracellular calcium stores with thapsigargin. Each of the foregoing techniques is well known to those of ordinary skill in the art and can be performed using various methods (see, e.g., Current Methods in Molecular Biology, eds. Ausubal, F.M., et al. 1987, Green Publishers and Wiley Interscience, N.Y.,
25 N.Y.). Exemplary methods are described herein.

Depletion of intracellular calcium stores is accomplished by treating the cells with 1 micromolar thapsigargin; alternative agents which function to deplete intracellular stores are described in by Putney, J.W. Jr., in Capacitative Calcium Entry, R.G. Landes Co. and Chapman & Hall, 1997 and include, for example, ionomycin, cyclopiazonic acid, and DBHQ.

30 Calcium influx is determined by measuring cytoplasmic calcium as indicated using the fura-2 fluorescent calcium indicator (see, e.g., G. Grynkiewicz, M. Poenie, R. Y. Tsien, A new generation of Ca²⁺ indicators with greatly improved fluorescence properties, J. Biol

Chem 260, 3440-50 (1985), and M. Poenie, R. Tsien, Fura-2: a powerful new tool for measuring and imaging $[Ca^{2+}]_i$ in single cells, Prog Clin Biol Res 210, 53-6 (1986)).

Patch Clamp Analysis and Determining Selectivity of SOC/CRAC

Patch clamp analysis of cells injected with SOC/CRAC cRNA is performed by using the general patch technique as described in Neher, E., "Ion channels for communication between and within cells", Science, 1992; 256:498-502. Specific techniques for applying the patch clamp analysis to RBL cells are described in Hoth, M., and Penner, R., "Depletion of intracellular calcium stores activates a calcium current in mast cells", Nature, 1992; 355:3535-355. Additional protocols for applying the patch clamp technique to other cell types are described in Putney, J.W. Jr., in Capacitative Calcium Entry, R.G. Landes Co. and Chapman & Hall, 1997

An exemplary protocol for patch clamp analysis of SOC/CRAC molecule expressed in RBL-2H3 mast cells using a recombinant vaccinia virus is as follows. The currents elicited by store depletion are determined using the whole cell configuration (Neher, E., Science, 1992; 256:498-502). Currents in SOC/CRAC expressing cells are compared to currents in control cells expressing an irrelevant protein or a classic Trp family calcium channel known as VR1 (M. J. Caterina, et al., The capsaicin receptor: a heat-activated ion channel in the pain pathway [see comments], Nature 389, 816-24 (1997)) in order to assess the contribution of SOC/CRAC expression. In addition, the magnitude of whole cell currents in the presence of extracellular calcium (10 mM), barium (10 mM), or magnesium (10 mM) are compared to determine the relative permeability of the channels to each of these ions (Hoth, M., and Penner, R., Nature, 1992; 355:3535-355) and, thereby, determine the ionic selectivity.

Pharmacologic Behavior of SOC/CRAC

For analysis of the pharmacologic behavior of a SOC/CRAC molecule, a SOC/CRAC molecule is expressed in RBL-2H3 mast cells using a recombinant vaccinia virus, and the degree of calcium influx elicited by store depletion is monitored using a bulk spectrofluorimeter or a fluorescence microscope and the calcium sensitive dye fura-2 (G. Grynkiewicz, M. Poenie, R. Y. Tsien, A new generation of Ca^{2+} indicators with greatly improved fluorescence properties, J Biol Chem 260, 3440-50 (1985) and M. Poenie, R. Tsien, Fura-2: a powerful new tool for measuring and imaging $[Ca^{2+}]_i$ in single cells, Prog Clin Biol Res 210, 53-6 (1986)). The level of cytoplasmic calcium in SOC/CRAC expressing cells is compared to the level achieved in control cells expressing an irrelevant protein or a classic Trp. family calcium channels known as VR1 (M. J. Caterina, et al., The

capsaicin receptor: a heat-activated ion channel in the pain pathway [see comments], Nature 389, 816-24 (1997)). These cells then are pre-incubated with the desired pharmacologic reagent, and again the response to store depletion is monitored. Comparison of the effect of depleting stores in SOC/CRAC expressing cells relative to controls in the presence or absence of the pharmacologic reagent is used to assess the ability of that reagent to modulate SOC/CRAC activity. Sphingosine is an exemplary molecule that can be used as pharmacologic reagents for pharmacologic characterization of SOC/CRAC calcium channels. See, e.g., Mathes, C., et al., Calcium release activated calcium current as a direct target for sphingosine, J Biol Chem 273(39):25020-25030 (1998). Other non-specific calcium channel inhibitors that can be used for this purpose include SKR96365 (Calbiochem) and Lanthanum.

Bulk Calcium Assays

Bulk calcium assays can be performed in a PTI Deltascan bulk spectrofluorometer using fura-2 as described in Scharenberg AM, et al., EMBO J, 1995, 14(14):3385-94.

Gene Targeting

The method (and reagents) described by Buerstedde JM et al, (Cell, 1991, Oct 4;67(1):179-88), was used to generate "knockouts" in cells. Briefly, part of the chicken SOC-2/CRAC-1 genomic sequence coding for the transmembrane region was cloned utilizing the human sequence as the probe in a chicken library screen. Chicken SOC-2/CRAC-1 clones were isolated and characterized using standard methodology. The putative exon and domain arrangement of the chicken SOC-2/CRAC-1, is depicted in Figure 1. The exons coding for TM5 (pore region) and TM6, were replaced with promoter/antibiotic cassettes (see Figure1). These targeting vectors were then used to target (and replace) the endogenous gene in DT-40 cells (chicken B lymphocyte cells).

Results

Example 1: Transient Expression of SOC/CRAC

In the above-identified cell lines and using both of the foregoing expression techniques, SOC/CRAC expression enhances thapsigargin-dependent influx. In addition, SOC/CRAC expression also enhances the amount of intracellular calcium stores. That this effect is likely due to SOC/CRAC acting as a plasma membrane calcium channel can be confirmed by producing an in-frame carboxy-terminal translational fusion with green fluorescent protein followed by confocal microscopy, revealing that SOC/CRAC is expressed predominantly as a plasma membrane calcium channel.

Example 2: Patch Clamp Analysis

The biophysical characteristics of SOC/CRAC enhanced currents when expressed in *Xenopus* oocytes are determined. SOC/CRAC cRNA injection is able to enhance thapsigargin-dependent whole cell currents. In addition, SOC/CRAC does not alter the reversal potential of these currents and the determination of the P_{Ca}/P_{Na} ratio shows that SOC/CRAC channels are highly calcium selective.

Example 3: *Pharmacologic Behavior of SOC/CRAC*

The pharmacologic behavior of SOC/CRAC is evaluated as described above. SOC/CRAC-enhanced influx is inhibited by sphingosine in a manner that is substantially the same as that of endogenous thapsigargin-dependent calcium influx.

Example 4: *Gene targeting*

Transfection of DT-40 cells with the foregoing targeting vectors, selection for antibiotic resistance, and screening, is collectively referred to, herein, as a round of targeting. For the first round of targeting SOC-2/CRAC-1, 18/24 clones with homologous recombination of the targeting construct into one of the endogenous SOC-2/CRAC-1 alleles were obtained. On the second round of targeting (in order to target the second allele and therefore generate a homozygous SOC-2/CRAC-1 mutant cell), 0/48 clones were obtained. These results indicate that a "null" SOC-2/CRAC-1 mutation is detrimental to DT-40 cells, and that SOC-2/CRAC-1 is required for cell viability.

Table I. Nucleotide Sequences with homologies to SOC/CRAC nucleic acids

Sequences with SEQ ID NOs and GenBank accession numbers:
SEQ ID NO:9, AB001535, AI226731, H18835, AA419592, AA261842, AA419407, AA592910, D86107, AI098310, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, AC005538, AA654650, AA370110, AA313170, AA493512, AI670079, AI671853.

Table II. Amino Acid Sequences with homologies to SOC/CRAC polypeptides

Sequences with SEQ ID NOs and GenBank accession numbers:
SEQ ID NO:10, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, AB001535, AA592910, D86107, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, NP003298, CAB00861, NP002411, CAA92726, CAB05572.

All references, patents, and patent documents disclosed herein are incorporated by reference herein in their entirety.

What is claimed is presented below and is followed by a Sequence Listing. We claim:

Claims

1. An isolated nucleic acid molecule, comprising:

(a) nucleic acid molecules which hybridize under stringent conditions to a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, and which code for a SOC/CRAC polypeptide;

(b) deletions, additions and substitutions of (a) which code for a respective SOC/CRAC polypeptide;

(c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) in codon sequence due to the degeneracy of the genetic code, and

(d) complements of (a), (b) or (c).

2. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:1.

3. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:27.

4. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:29.

5. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:31.

6. An isolated nucleic acid molecule selected from the group consisting of

(a) a unique fragment of a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:29, and SEQ ID NO:31,

(b) complements of (a),

provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to any sequence selected from a sequence group consisting of

(1) sequences having the SEQ. ID NOS. or GenBank accession numbers of Table I,

(2) complements of (1), and

(3) fragments of (1) and (2).

7. The isolated nucleic acid molecule of claim 6, wherein the sequence of contiguous nucleotides is selected from the group consisting of:

- (1) at least two contiguous nucleotides nonidentical to the sequence group,
- (2) at least three contiguous nucleotides nonidentical to the sequence group,
- 5 (3) at least four contiguous nucleotides nonidentical to the sequence group,
- (4) at least five contiguous nucleotides nonidentical to the sequence group,
- (5) at least six contiguous nucleotides nonidentical to the sequence group,
- (6) at least seven contiguous nucleotides nonidentical to the sequence group.

10 8. The isolated nucleic acid molecule of claim 6, wherein the unique fragment has a size selected from the group consisting of at least: 8 nucleotides, 10 nucleotides, 12 nucleotides, 14 nucleotides, 16 nucleotides, 18 nucleotides, 20, nucleotides, 22 nucleotides, 24 nucleotides, 26 nucleotides, 28 nucleotides, 30 nucleotides, 50 nucleotides, 75 nucleotides, 100 nucleotides, and 200 nucleotides.

15 9. The isolated nucleic acid molecule of claim 6, wherein the molecule encodes a polypeptide which is immunogenic.

10. An expression vector comprising the isolated nucleic acid molecule of claims 1, 2, 3, 4, 5, 6, 7, 8, or 9 operably linked to a promoter.

11. A host cell transformed or transfected with the expression vector of claim 10.

20 12. An isolated polypeptide encoded by the isolated nucleic acid molecule according to anyone of claims 1 or 6, wherein the polypeptide comprises a SOC/CRAC polypeptide or a unique fragment thereof.

13. The isolated polypeptide of claim 12, wherein the isolated polypeptide is encoded by the isolated nucleic acid molecule of claim 2, 3, 4, or 5.

25 14. The isolated polypeptide of claim 13, wherein the isolated polypeptide comprises a polypeptide having the sequence of amino acids selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32.

15. An isolated polypeptide encoded by the isolated nucleic acid molecule of claim 1, 2, 3, 4, or 5, wherein the polypeptide, or unique fragment thereof is immunogenic.

16. An isolated binding polypeptide which binds selectively to a polypeptide encoded by the isolated nucleic acid molecule of claim 1, 2, 3, 4, or 5.

5 17. The isolated binding polypeptide of claim 16, wherein the isolated binding polypeptide binds to a polypeptide having the sequence of amino acids selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32.

10 18. The isolated binding polypeptide of claim 17, wherein the isolated binding polypeptide is an antibody or an antibody fragment selected from the group consisting of a Fab fragment, a F(ab)₂ fragment or a fragment including a CDR3 region selective for the polypeptide.

15 19. An isolated polypeptide, comprising a unique fragment of the polypeptide of claim 12 of sufficient length to represent a sequence unique within the human genome, provided that the fragment excludes a sequence of contiguous amino acids identified in Table II.

20. A method for isolating a SOC/CRAC molecule having SOC/CRAC calcium channel activity, comprising:

20 a) contacting a binding molecule that is a SOC/CRAC nucleic acid or a SOC/CRAC binding polypeptide with a sample containing one or more SOC/CRAC molecules, under conditions sufficient to form a complex of the SOC/CRAC nucleic acid or the SOC/CRAC binding polypeptide and the SOC/CRAC molecule;

b) detecting the presence of the complex;

c) isolating the SOC/CRAC molecule from the complex; and

25 d) determining whether the isolated SOC/CRAC molecule has SOC/CRAC calcium channel activity.

21. The method of claim 20, wherein the binding molecule is a SOC/CRAC nucleic acid.

22. The method of claim 20, wherein the binding molecule is a SOC/CRAC binding polypeptide.

23. The method of claim 21, wherein the SOC/CRAC nucleic acid comprises at least 14 nucleotides from any contiguous portion of a sequence of nucleotides selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31.

5 24. A method for identifying agents useful in the modulation of SOC/CRAC calcium channel activity, comprising:

a) contacting a SOC/CRAC polypeptide with a candidate agent suspected of modulating SOC/CRAC calcium channel activity, under conditions sufficient to allow the SOC/CRAC polypeptide to interact selectively with the candidate agent;

10 b) detecting a Ca^{2+} concentration associated with SOC/CRAC calcium channel activity of the SOC/CRAC polypeptide in the presence of the candidate agent; and

c) comparing the Ca^{2+} concentration of step (b) with a control Ca^{2+} concentration of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the candidate agent modulates SOC/CRAC calcium channel activity.

15

25. A method for determining the level of SOC/CRAC expression in a subject, comprising:

a) measuring the expression of SOC/CRAC in a test sample obtained from the subject, and

20 b) comparing the measured expression of SOC/CRAC in the test sample to the expression of the SOC/CRAC polypeptide in a control to determine the level of SOC/CRAC expression in the subject.

25

26. The method of claim 25, wherein the expression of SOC/CRAC in (b) is SOC/CRAC mRNA expression.

27. The method of claim 25, wherein the expression of SOC/CRAC in (b) is SOC/CRAC polypeptide expression.

28. The method of claim 25, wherein the test sample is tissue.

29. The method of claim 25, wherein the test sample is a biological fluid.

-52-

30. The method of claim 26, wherein SOC/CRAC mRNA expression is measured using the Polymerase Chain Reaction (PCR).

31. The method of claim 26, wherein SOC/CRAC mRNA expression is measured using a method selected from the group consisting of northern blotting, monoclonal antisera to SOC/CRAC and polyclonal antisera to SOC/CRAC.

32. A kit, comprising a package containing:

an agent that selectively binds to the isolated nucleic acid of claim 1 or an expression product thereof, and

a control for comparing to a measured value of binding of said agent to said isolated nucleic acid of claim 1 or expression product thereof.

33. The kit of claim 32, wherein the control comprises an epitope of the expression product of the nucleic acid of claim 1.

34. A pharmaceutical composition comprising:

a pharmaceutically effective amount of an agent comprising of an isolated nucleic acid molecule of claim 1 or an expression product thereof, and

a pharmaceutically acceptable carrier.

35. The pharmaceutical composition of claim 34, wherein the agent is an expression product of the isolated nucleic acid molecule of claim 1.

36. A method for identifying agents useful in the modulation of a SOC/CRAC polypeptide kinase activity, comprising:

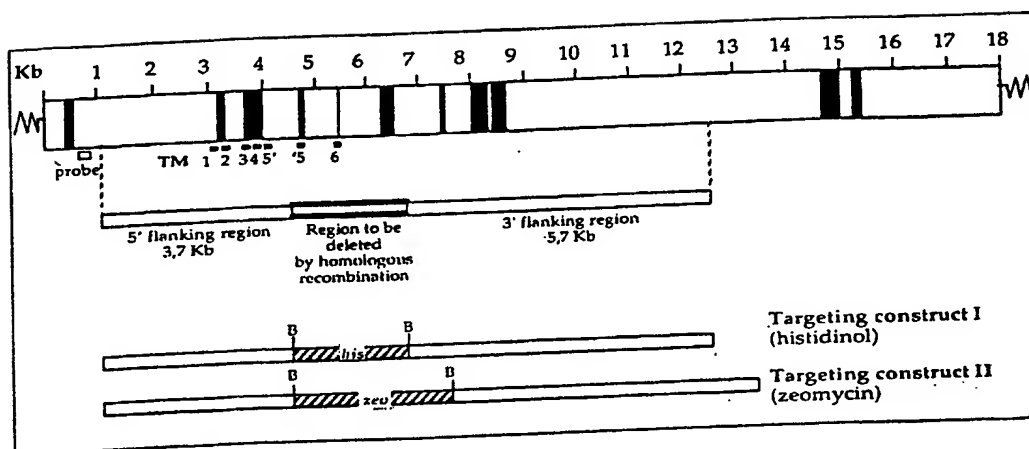
a) contacting a SOC/CRAC polypeptide with kinase activity with a candidate agent suspected of modulating SOC/CRAC kinase activity, under conditions sufficient to allow the candidate agent to interact with the SOC/CRAC polypeptide and modulate its kinase activity;

b) detecting a kinase activity associated with the SOC/CRAC polypeptide in the presence of the candidate agent; and

c) comparing the kinase activity of step (b) with a control kinase activity of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the candidate agent modulates SOC/CRAC kinase activity.

37. The method of claim 36, wherein the SOC/CRAC polypeptide comprises amino acids 999-1180 of the sequence represented as SEQ ID NO:24, or a fragment thereof that retains the kinase activity.

FIGURE 1.



-1-

SEQUENCE LISTING

<110> Beth Israel Deaconess Medical Center, Inc.
Scharenberg, Andrew

<120> CHARACTERIZATION OF A CALCIUM CHANNEL FAMILY

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<211> 141

<212> PRT

<213> Homo Sapiens

<400> 2

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			20					25						30	

-2-

Ala Thr Glu Gly Asp Asn Thr Glu Phe Gly Ala Phe Val Gly His Arg
 35 40 45
 Asp Ser Met Asp Leu Gln Arg Phe Lys Glu Thr Ser Asn Lys Ile Lys
 50 55 60
 Ile Leu Ser Asn Asn Asn Thr Ser Glu Asn Thr Leu Lys Arg Val Ser
 65 70 75 80
 Ser Leu Ala Gly Phe Thr Asp Cys His Arg Thr Ser Ile Pro Val His
 85 90 95
 Ser Lys Gln Glu Lys Ile Ser Arg Arg Pro Ser Thr Glu Asp Thr His
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 Glu Val Asp Ser Lys Ala Ala Leu Ile Pro Val Cys Arg Phe Gln Leu
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 gactccattt cttcaagcag tctacctctt tgwacagtat atcattatgg ttaatcttct 180
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-3-

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<222> (68)...(68)

<223> UNKNOWN

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			20					25					30		
Phe	Leu	Gln	Ala	Val	Tyr	Leu	Phe	Xaa	Gln	Tyr	Ile	Ile	Met	Val	Asn
		35					40					45			
Leu	Leu	Ile	Ala	Phe	Xaa	Asn	Asn	Val	Tyr	Leu	Gln	Val	Lys	Ala	Ile
		50				55					60				
Ser	Asn	Ile	Xaa	Trp	Lys	Tyr	Gln	Arg	Tyr	His	Phe	Ile	Met	Ala	Tyr
65					70					75				80	
His	Glu	Lys	Pro	Val	Leu	Pro	Pro	Pro	Leu	Ile	Ile	Leu	Ser	His	Ile
				85					90					95	
Val	Ser	Leu	Phe	Cys	Cys	Ile	Cys	Lys	Arg	Arg	Lys	Lys	Asp	Lys	Thr
			100					105					110		
Ser	Asp	Gly	Pro	Lys	Leu	Phe	Leu	Thr	Glu	Glu	Asp	Gln	Lys	Lys	Leu
		115					120					125			
His	Asp	Phe	Glu	Glu	Gln	Cys	Val	Glu	Met	Tyr	Phe	Asn	Glu	Lys	Asp
	130					135					140				
Asp	Lys	Phe	His	Ser	Gly	Ser	Glu	Glu	Arg	Ile	Arg	Val	Thr	Phe	Glu
					150					155					160
Arg	Val	Glu	Gln	Met	Cys	Ile	Gln	Ile	Lys	Glu	Val	Gly	Asp	Pro	Cys
				165					170					175	
Gln	Leu	His	Lys	Lys	Ile	Ile	Thr	Ile	Ile	Arg	Phe	Ser	Asn	Trp	Pro
			180					185					190		
Phe	Ala	Arg	Ser	Phe	Ser	Pro	Asp	Gly	Arg	Tyr	Ile	Lys	Asn	Thr	His
		195				200						205			
Trp	Pro	Lys	Ala	Ser	Glu	Ala	Ser	Lys	Val	His	Asn	Glu	Ile	Thr	Arg
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Glu	Leu	Ser	Ile	Ser	Lys	His	Leu	Ala	Gln	Asn					
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<211> 1579

<212> DNA

<213> Homo Sapiens

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<221> unsure

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<223> g or c

<221> unsure

<222> (372)...(372)

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<221> unsure

<222> (374)...(374)

<223> g or a

<221> unsure

<222> (375)...(375)

<223> g or c

-4-

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gtcatccsca	csarscaaat	tttttgntag	tacaccatct	cagccaagtt	gcaaaaagcca	420
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			20					25					30		
Cys	Asn	Ile	Phe	Gly	Gln	Asp	Leu	Pro	Ala	Val	Pro	Gln	Arg	Lys	Glu
		35					40					45			

-5-

Phe Asn Phe Pro Glu Ala Gly Ser Ser Ser Gly Ala Leu Phe Pro Ser
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 Ala Val Ser Pro Pro Glu Leu Arg Gln Arg Leu His Gly Val Glu Leu
 65 70 75 80
 Leu Lys Ile Phe Asn Lys Asn Gln Lys Leu Gly Ser Ser Ser Thr Ser
 85 90 95
 Ile Pro His Leu Ser Ser Xaa Xaa Xaa Lys Phe Phe Xaa Ser Thr Pro
 100 105 110
 Ser Gln Pro Ser Cys Lys Ser His Leu Glu Thr Gly Thr Lys Asp Gln
 115 120 125
 Glu Thr Val Cys Ser Lys Ala Thr Glu Gly Asp Asn Xaa Glu Phe Gly
 130 135 140
 Ala Phe Val Gly His Arg Asp Ser Met Asp Leu Gln Arg Phe Lys Glu
 145 150 155 160
 Thr Ser Asn Lys Ile Lys Ile Leu Ser Asn Asn Asn Thr Ser Glu Asn
 165 170 175
 Thr Leu Lys Arg Val Ser Ser Leu Ala Gly Phe Thr Asp Cys His Arg
 180 185 190
 Thr Ser Ile Pro Val His Ser Lys Gln Glu Lys Ile Ser Arg Arg Pro
 195 200 205
 Ser Thr Glu Asp Thr His Glu Val Asp Ser Lys Ala Ala Leu Ile Pro
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<210> 7

<211> 3532

<212> DNA

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<220>

<221> unsure

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gtcacttttg aaagagtggg gcagatgagc attcagatta aagaagttgg agatcgtgtc	300
aactacataa aaagatcatt acagtcctta gattctcaaa ttgggtcatct gcaagatctc	360

-6-

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 <212> PRT
 <213> Mus Musculus

<400> 8

-7-

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 Lys Asp Lys Thr Ser Asp Gly Pro Lys Leu Phe Leu Thr Glu Glu Asp
 35 40 45
 Gln Lys Lys Leu His Asp Phe Glu Glu Gln Cys Val Glu Met Tyr Phe
 50 55 60
 Asp Glu Lys Asp Asp Lys Phe Asn Ser Gly Ser Glu Glu Arg Ile Arg
 65 70 75 80
 Val Thr Phe Glu Arg Val Glu Gln Met Ser Ile Gln Ile Lys Glu Val
 85 90 95
 Gly Asp Arg Val Asn Tyr Ile Lys Arg Ser Leu Gln Ser Leu Asp Ser
 100 105 110
 Gln Ile Gly His Leu Gln Asp Leu Ser Ala Leu Thr Val Asp Thr Leu
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 145 150 155 160
 Ile Asp Asp Val Pro Val Arg Pro Leu Trp Glu Glu Pro Ser Ala Val
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 180 185 190
 Pro Phe Leu Cys Asn Ile Phe Met Lys Asp Glu Lys Asp Pro Gln Tyr
 195 200 205
 Asn Leu Phe Gly Gln Asp Leu Pro Val Ile Pro Gln Arg Lys Glu Phe
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 225 230 235 240
 Val Ser Pro Pro Glu Leu Arg Gln Arg Arg His Gly Val Glu Met Leu
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 Lys Ile Phe Asn Lys Asn Gln Lys Leu Gly Ser Ser Pro Asn Ser Ser
 260 265 270
 Pro His Met Ser Ser Pro Pro Thr Lys Phe Ser Val Ser Thr Pro Ser
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 Gln Pro Ser Cys Lys Ser His Leu Glu Ser Thr Thr Lys Asp Gln Glu
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 305 310 315 320
 Phe Val Gly His Arg Asp Ser Met Asp Leu Gln Arg Phe Lys Glu Thr
 325 330 335
 Ser Asn Lys Ile Arg Glu Leu Leu Ser Asn Asp Thr Pro Glu Asn Thr
 340 345 350
 Leu Lys His Val Gly Ala Ala Gly Tyr Ser Glu Cys Cys Lys Thr Ser
 355 360 365
 Thr Ser Leu His Ser Val Gln Ala Glu Ser Cys Ser Arg Arg Ala Ser
 370 375 380
 Thr Glu Asp Ser Pro Glu Val Asp Ser Lys Ala Ala Leu Leu Pro Asp
 385 390 395 400
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 405 410 415
 Thr Leu Asn Gly Leu Ala Ser Pro Phe Lys Pro Val Leu Asp Thr Asn
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 Tyr Tyr Tyr Ser Ala Val Glu Arg Asn Asn Leu Met Arg Leu Ser Gln
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 <222> (5094) ... (5094)
 <223> unknown

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-10-

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-11-

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-12-

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-13-

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-15-

<212> PRT

<213> Homo Sapiens

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Glu Asn Ile Lys Lys Lys Glu Cys Val Tyr Phe Val Glu Ser Ser Lys
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Leu Ser Asp Ala Gly Lys Val Val Cys Gln Cys Gly Tyr Thr His Glu
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Gln His Leu Glu Glu Ala Thr Lys Pro His Thr Phe Gln Gly Thr Gln
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Trp Asp Pro Lys Lys His Val Gln Glu Met Pro Thr Asp Ala Phe Gly
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Asp Ile Val Phe Thr Gly Leu Ser Gln Lys Val Lys Lys Tyr Val Arg
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Val Ser Gln Asp Thr Pro Ser Ser Val Ile Tyr His Leu Met Thr Gln
145          150          155          160
His Trp Gly Leu Asp Val Pro Asn Leu Leu Ile Ser Val Thr Gly Gly
165          170          175
Ala Lys Asn Phe Asn Met Lys Pro Arg Leu Lys Ser Ile Phe Arg Arg
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Gly Leu Val Lys Val Ala Gln Thr Thr Gly Ala Trp Ile Ile Thr Gly
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Gly Ser His Thr Gly Val Met Lys Gln Val Gly Glu Ala Val Arg Asp
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Phe Ser Leu Ser Ser Ser Tyr Lys Glu Gly Glu Leu Ile Thr Ile Gly
225          230          235          240
Val Ala Thr Trp Gly Thr Val His Arg Arg Glu Gly Leu Ile His Pro
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Thr Gly Ser Phe Pro Ala Glu Tyr Ile Leu Asp Glu Asp Gly Gln Gly
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Asp Gly Thr His Gly Gln Tyr Gly Val Glu Ile Pro Leu Arg Thr Arg
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Ile Lys Ile Pro Ile Val Cys Val Val Leu Glu Gly Gly Pro Gly Thr
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Val Glu Gly Ser Gly Arg Val Ala Asp Val Ile Ala Gln Val Ala Asn
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Val Phe Phe Gln Glu Met Phe Glu Thr Phe Thr Glu Ser Arg Ile Val
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Glu Trp Thr Lys Lys Ile Gln Asp Ile Val Arg Arg Arg Gln Leu Leu
405          410          415
Thr Val Phe Arg Glu Gly Lys Asp Gly Gln Gln Asp Val Asp Val Ala
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Ile Leu Gln Ala Leu Leu Lys Ala Ser Arg Ser Gln Asp His Phe Gly
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-16-

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 Pro Ser Asp Leu His Pro Thr Met Thr Ala Ala Leu Ile Ser Asn Lys
 485 490 495
 Pro Glu Phe Val Lys Leu Phe Leu Glu Asn Gly Val Gln Leu Lys Glu
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 Phe Val Thr Trp Asp Thr Leu Leu Tyr Leu Tyr Glu Asn Leu Asp Pro
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 Ser Cys Leu Phe His Ser Lys Leu Gln Lys Val Leu Val Glu Asp Pro
 530 535 540
 Glu Arg Pro Ala Cys Ala Pro Ala Ala Pro Arg Leu Gln Met His His
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 Val Ala Gln Val Leu Arg Glu Leu Leu Gly Asp Phe Thr Gln Pro Leu
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 Tyr Pro Arg Pro Arg His Asn Asp Arg Leu Arg Leu Leu Leu Pro Val
 580 585 590
 Pro His Val Lys Leu Asn Val Gln Gly Val Ser Leu Arg Ser Leu Tyr
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 Lys Arg Ser Ser Gly His Val Thr Phe Thr Met Asp Pro Ile Arg Asp
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 Glu Glu Met Leu Ala Leu Ala Glu Glu Tyr Glu His Arg Ala Ile Gly
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 Val Phe Thr Glu Cys Tyr Arg Lys Asp Glu Glu Arg Ala Gln Lys Leu
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 Ser Asp Phe Trp Asn Lys Leu Asp Val Gly Ala Ile Leu Leu Phe Val
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 Ala Gly Leu Thr Cys Arg Leu Ile Pro Ala Thr Leu Tyr Pro Gly Arg
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-17-

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 Glu Pro Gly Glu Met Leu Pro Arg Lys Leu Lys Arg Ile Leu Arg Gln
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-18-

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 Cys Ser Tyr Phe Val Pro Ser Gln Arg Phe Ser Glu Arg Cys Gly Cys
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 Ala Arg Ile Ser Phe Asp Ser Asp Pro Arg Asp Ile Val His Leu Met
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 Gly Gly Leu Thr Lys Phe Asp Leu Gln Pro Lys Leu Ala Arg Thr Phe

-19-

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 Arg Glu Ser Asp Asp Glu Asp Asp Phe Ser Asn Leu Glu Glu Glu Ala

-20-

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Glu	Asp	Thr	Asp	Thr	Ser	Ser	Asp	Ser	Ser	Ser	Asp	Ser	Asp	Asp	Ser
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-21-

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 Gly Tyr Trp Ile Ala Pro Val Gly Leu Thr Val Phe Met Leu Ala Thr
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 Asn Val Leu Leu Met Asn Val Met Val Ala Gly Cys Thr Tyr Ile Phe
 1445 1450 1455
 Glu Lys His Ile Gln Ser Thr Arg Glu Ile Phe Leu Phe Glu Arg Tyr
 1460 1465 1470
 Gly Gln Val Met Glu Tyr Glu Ser Thr Pro Trp Leu Pro Pro Pro Phe
 1475 1480 1485
 Thr Ile Ile Tyr His Val Ile Trp Leu Phe Lys Leu Ile Lys Ser Ser
 1490 1495 1500
 Ser Arg Met Phe Glu Arg Lys Asn Leu Phe Asp Gln Ser Leu Lys Leu
 1505 1510 1515 152
 Phe Leu Ser Pro Asp Glu Met Glu Lys Val His Thr Phe Glu Glu Glu
 1525 1530 1535
 Ser Val Glu Asp Met Lys Arg Glu Thr Glu Lys Lys Asn Leu Ser Ser
 1540 1545 1550
 Asn Asp Glu Arg Ile His Arg Thr Ala Glu Arg Thr Asp Ala Ile Leu
 1555 1560 1565
 Asn Arg Val Ser His Leu Thr Gln Leu Glu Phe Thr Leu Lys Glu Glu
 1570 1575 1580
 Ile Arg Glu Leu Glu His Lys Met Lys Asn Met Asp Ser Arg His Lys
 1585 1590 1595 160
 Glu Gln Met Asn Leu Met Leu Asp Met Asn Lys Lys Leu Gly Lys Phe
 1605 1610 1615
 Ile Ser Gly Lys Tyr Lys Arg Gly Ser Phe Gly Gly Ser Gly Ser Asp
 1620 1625 1630
 Gly Gly Gly Gly Ser Ser Asp Asn Ser Lys Leu Glu Pro Asn Asn Ser
 1635 1640 1645
 Val Pro Met Ile Thr Val Asp Gly Pro Ser Pro Ile Gly Ser Arg Arg
 1650 1655 1660
 Thr Ser Gly Gln Tyr Leu Lys Arg Asp Ser Leu Gln Ala Lys Lys Lys
 1665 1670 1675 168
 Ile Thr Glu Asn Arg Arg Ser Ser Leu Glu Gln Pro Lys Ile Pro Ser
 1685 1690 1695
 Ile Gln Phe Asn Leu Met Glu Asp Gln Asp Glu Ser Ala Ala Glu Ser
 1700 1705 1710
 Ala Thr Glu Glu Val Ser Ile Ser Ile Pro Val Pro Gln Met Arg Val
 1715 1720 1725
 Arg Gln Val Thr Glu Ser Asp Lys Ser Asp Leu Ser Glu Asp Asp Leu
 1730 1735 1740
 Ile Thr Arg Glu Asp Ala Pro Pro Thr Ser Ile Asn Leu Pro Arg Gly
 1745 1750 1755 176
 Pro Arg Arg His Ala Leu Tyr Ser Thr Ile Ala Asp Ala Ile Glu Thr

-22-

1765 1770 1775
 Glu Asp Asp Phe Tyr Ala Asp Ser Pro Val Pro Met Pro Met Thr Pro
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 Gln Arg Asp Asp Ser Asp Tyr Glu
 1810 1815

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 <211> 1387
 <212> PRT
 <213> C. Elegans

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 35 40 45
 Ser Phe Arg Ser Asp His Leu Ser Arg Lys Ser Thr His Lys Phe Leu
 50 55 60
 Asp Asn Pro Asn Leu Phe Ala Ile Glu Leu Thr Glu Lys Leu Ser Pro
 65 70 75 80
 Pro Trp Ile Glu Asn Thr Phe Glu Lys Arg Glu Cys Ile Arg Phe Ala
 85 90 95
 Ala Leu Pro Lys Asp Pro Glu Arg Cys Gly Cys Gly Arg Pro Leu Ser
 100 105 110
 Ala His Thr Pro Ala Ser Thr Phe Phe Ser Thr Leu Pro Val His Leu
 115 120 125
 Leu Glu Lys Glu Gln Gln Thr Trp Thr Ile Ala Asn Asn Thr Gln Thr
 130 135 140
 Ser Thr Thr Asp Ala Phe Gly Thr Ile Val Phe Gln Gly Gly Ala His
 145 150 155 160
 Ala His Lys Ala Gln Tyr Val Arg Leu Ser Tyr Asp Ser Glu Pro Leu
 165 170 175
 Asp Val Met Tyr Leu Met Glu Lys Val Trp Gly Leu Glu Ala Pro Arg
 180 185 190
 Leu Val Ile Thr Val His Gly Gly Met Ser Asn Phe Glu Leu Glu Glu
 195 200 205
 Arg Leu Gly Arg Leu Phe Arg Lys Gly Met Leu Lys Ala Ala Gln Thr
 210 215 220
 Thr Gly Ala Trp Ile Ile Thr Ser Gly Leu Asp Ser Gly Val Val Arg
 225 230 235 240
 His Val Ala Lys Ala Leu Asp Glu Ala Gly Ile Ser Ala Arg Met Arg
 245 250 255
 Ser Gln Ile Val Thr Ile Gly Ile Ala Pro Trp Gly Val Ile Lys Arg
 260 265 270
 Lys Glu Arg Leu Ile Arg Gln Asn Glu His Val Tyr Tyr Asp Val His
 275 280 285
 Ser Leu Ser Val Asn Ala Asn Val Gly Ile Leu Asn Asp Arg His Ser
 290 295 300
 Tyr Phe Leu Leu Ala Asp Asn Gly Thr Val Gly Arg Phe Gly Ala Asp
 305 310 315 320
 Leu His Leu Arg Gln Asn Leu Glu Asn His Ile Ala Thr Phe Gly Cys
 325 330 335
 Asn Gly Arg Lys Val Pro Val Val Cys Thr Leu Leu Glu Gly Gly Ile
 340 345 350
 Ser Ser Ile Asn Ala Ile His Asp Tyr Val Thr Met Lys Pro Asp Ile
 355 360 365

-23-

Pro Ala Ile Val Cys Asp Gly Ser Gly Arg Ala Ala Asp Ile Ile Ser
 370 375 380
 Phe Ala Ala Arg Tyr Ile Asn Ser Asp Gly Thr Phe Ala Ala Glu Val
 385 390 395 400
 Gly Glu Lys Leu Arg Asn Leu Ile Lys Met Val Phe Pro Glu Thr Asp
 405 410 415
 Gln Glu Glu Met Phe Arg Lys Ile Thr Glu Cys Val Ile Arg Asp Asp
 420 425 430
 Leu Leu Arg Ile Phe Arg Tyr Gly Gln Glu Glu Glu Glu Asp Val Asp
 435 440 445
 Phe Val Ile Leu Ser Thr Val Leu Gln Lys Gln Asn Leu Pro Pro Asp
 450 455 460
 Glu Gln Leu Ala Leu Thr Leu Ser Trp Asn Arg Val Asp Leu Ala Lys
 465 470 475 480
 Ser Cys Leu Phe Ser Asn Gly Arg Lys Trp Ser Ser Asp Val Leu Glu
 485 490 495
 Lys Ala Met Asn Asp Ala Leu Tyr Trp Asp Arg Val Asp Phe Val Glu
 500 505 510
 Cys Leu Leu Glu Asn Gly Val Ser Met Lys Asn Phe Leu Ser Ile Asn
 515 520 525
 Arg Leu Glu Asn Leu Tyr Asn Met Asp Asp Ile Asn Ser Ala His Ser
 530 535 540
 Val Arg Asn Trp Met Glu Asn Phe Asp Ser Met Asp Pro His Thr Tyr
 545 550 555 560
 Leu Thr Ile Pro Met Ile Gly Gln Val Val Glu Lys Leu Met Gly Asn
 565 570 575
 Ala Phe Gln Leu Tyr Tyr Thr Ser Arg Ser Phe Lys Gly Lys Tyr Asp
 580 585 590
 Arg Tyr Lys Arg Ile Asn Gln Ser Ser Tyr Phe His Arg Lys Arg Lys
 595 600 605
 Ile Val Gln Lys Glu Leu Phe Lys Lys Lys Ser Asp Asp Gln Ile Asn
 610 615 620
 Asp Asn Glu Glu Glu Asp Phe Ser Phe Ala Tyr Pro Phe Asn Asp Leu
 625 630 635 640
 Leu Ile Trp Ala Val Leu Thr Ser Arg His Gly Met Ala Glu Cys Met
 645 650 655
 Trp Val His Gly Glu Asp Ala Met Ala Lys Cys Leu Leu Ala Ile Arg
 660 665 670
 Leu Tyr Lys Ala Thr Ala Lys Ile Ala Glu Asp Glu Tyr Leu Asp Val
 675 680 685
 Glu Glu Ala Lys Arg Leu Phe Asp Asn Ala Val Lys Cys Arg Glu Asp
 690 695 700
 Ala Ile Glu Leu Leu Asp Gln Cys Tyr Arg Ala Asp His Asp Arg Thr
 705 710 715 720
 Leu Arg Leu Leu Arg Met Glu Leu Pro His Trp Gly Asn Asn Asn Cys
 725 730 735
 Leu Ser Leu Ala Val Leu Ala Asn Thr Lys Thr Phe Leu Ala His Pro
 740 745 750
 Cys Cys Gln Ile Leu Leu Ala Glu Leu Trp His Gly Ser Leu Lys Val
 755 760 765
 Arg Ser Gly Ser Asn Val Arg Val Leu Thr Ala Leu Ile Cys Pro Pro
 770 775 780
 Ala Ile Leu Phe Met Ala Tyr Lys Pro Lys His Ser Lys Thr Ala Arg
 785 790 795 800
 Leu Leu Ser Glu Glu Thr Pro Glu Gln Leu Pro Tyr Pro Arg Glu Ser
 805 810 815
 Ile Thr Ser Thr Thr Ser Asn Arg Tyr Arg Tyr Ser Lys Gly Pro Glu
 820 825 830
 Glu Gln Lys Glu Thr Leu Leu Glu Lys Gly Ser Tyr Thr Lys Lys Val
 835 840 845

-24-

Thr Ile Ile Ser Ser Arg Lys Asn Ser Gly Val Ala Ser Val Tyr Gly
 850 855 860
 Ser Ala Ser Ser Met Met Phe Lys Arg Glu Pro Gln Leu Asn Lys Phe
 865 870 875 880
 Glu Arg Phe Arg Ala Phe Tyr Ser Ser Pro Ile Thr Lys Phe Trp Ser
 885 890 895
 Trp Cys Ile Ala Phe Leu Ile Phe Leu Thr Thr Gln Thr Cys Ile Leu
 900 905 910
 Leu Leu Glu Thr Ser Leu Lys Pro Ser Lys Tyr Glu Trp Ile Thr Phe
 915 920 925
 Ile Tyr Thr Val Thr Leu Ser Val Glu His Ile Arg Lys Leu Met Thr
 930 935 940
 Ser Glu Gly Ser Arg Ile Asn Glu Lys Val Lys Val Phe Tyr Ala Lys
 945 950 955 960
 Trp Tyr Asn Ile Trp Thr Ser Ala Ala Leu Leu Phe Phe Leu Val Gly
 965 970 975
 Tyr Gly Phe Arg Leu Val Pro Met Tyr Arg His Ser Trp Gly Arg Val
 980 985 990
 Leu Leu Ser Phe Ser Asn Val Leu Phe Tyr Met Lys Ile Phe Glu Tyr
 995 1000 1005
 Leu Ser Val His Pro Leu Leu Gly Pro Tyr Ile Gln Met Ala Ala Lys
 1010 1015 1020
 Met Val Trp Ser Met Cys Tyr Ile Cys Val Leu Leu Leu Val Pro Leu
 1025 1030 1035 104
 Met Ala Phe Gly Val Asn Arg Gln Ala Leu Thr Glu Pro Asn Val Lys
 1045 1050 1055
 Asp Trp His Trp Leu Leu Val Arg Asn Ile Phe Tyr Lys Pro Tyr Phe
 1060 1065 1070
 Met Leu Tyr Gly Glu Val Tyr Ala Gly Glu Ile Asp Thr Cys Gly Asp
 1075 1080 1085
 Glu Gly Ile Arg Cys Phe Pro Gly Tyr Phe Ile Pro Pro Leu Leu Met
 1090 1095 1100
 Val Ile Phe Leu Leu Val Ala Asn Ile Leu Leu Leu Asn Leu Leu Ile
 1105 1110 1115 112
 Ala Ile Phe Asn Asn Ile Tyr Asn Asp Ser Ile Glu Lys Ser Lys Glu
 1125 1130 1135
 Ile Trp Leu Phe Gln Arg Tyr Gln Gln Leu Met Glu Tyr His Asp Ser
 1140 1145 1150
 Pro Phe Leu Pro Pro Pro Phe Ser Ile Phe Ala His Val Tyr His Phe
 1155 1160 1165
 Ile Asp Tyr Leu Tyr Asn Leu Arg Arg Pro Asp Thr Lys Arg Phe Arg
 1170 1175 1180
 Ser Glu His Ser Ile Lys Leu Ser Val Thr Glu Asp Glu Met Lys Arg
 1185 1190 1195 120
 Ile Gln Asp Phe Glu Glu Asp Cys Ile Asp Thr Leu Thr Arg Ile Arg
 1205 1210 1215
 Lys Leu Lys Leu Asn Thr Lys Glu Pro Leu Ser Val Thr Asp Leu Thr
 1220 1225 1230
 Glu Leu Thr Cys Gln Arg Val His Asp Leu Met Gln Glu Asn Phe Leu
 1235 1240 1245
 Leu Lys Ser Arg Val Tyr Asp Ile Glu Thr Lys Ile Asp His Ile Ser
 1250 1255 1260
 Asn Ser Ser Asp Glu Val Val Gln Ile Leu Lys Asn Lys Lys Leu Ser
 1265 1270 1275 128
 Gln Asn Phe Ala Ala Ser Ser Leu Ser Leu Pro Asp Thr Ser Ile Glu
 1285 1290 1295
 Val Pro Lys Ile Thr Lys Thr Leu Ile Asp Cys His Leu Ser Pro Val
 1300 1305 1310
 Ser Ile Glu Asp Arg Leu Ala Thr Arg Ser Pro Leu Leu Ala Asn Leu
 1315 1320 1325

-25-

Gln Arg Asp His Thr Leu Arg Lys Leu Pro Thr Trp Glu Thr Ser Thr
 1330 1335 1340
 Ala Ser Thr Ser Ser Phe Glu Phe Val Phe Tyr Phe Thr Arg His Glu
 1345 1350 1355 136
 Gly Asn Glu Asn Lys Tyr Glu Phe Lys Lys Leu Glu Lys Gly Gly Phe
 1365 1370 1375
 Trp Arg Asn Asn Tyr Val Ile Ser Trp Arg Leu
 1380 1385

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 <211> 1868
 <212> PRT
 <213> C. Elegans

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 Trp Cys Thr Met Glu Ser Asp Glu Leu Gly Val Thr Arg Tyr Leu Gln
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 Ser Lys Gly Gly Asp Gln Val Pro Pro Thr Ser Thr Thr Thr Gly Gly
 35 40 45
 Ala Gly Gly Asp Gly Asn Ala Val Pro Thr Thr Ser Gln Ala Gln Ala
 50 55 60
 Gln Thr Phe Asn Ser Gly Arg Gln Thr Thr Gly Met Ser Ser Gly Asp
 65 70 75 80
 Arg Leu Asn Glu Asp Val Ser Ala Thr Ala Asn Ser Ala Gln Leu Val
 85 90 95
 Leu Pro Thr Pro Leu Phe Asn Gln Met Arg Phe Thr Glu Ser Asn Met
 100 105 110
 Ser Leu Asn Arg His Asn Trp Val Arg Glu Thr Phe Thr Arg Arg Glu
 115 120 125
 Cys Ser Arg Phe Ile Ala Ser Ser Arg Asp Leu His Lys Cys Gly Cys
 130 135 140
 Gly Arg Thr Arg Asp Ala His Arg Asn Ile Pro Glu Leu Thr Ser Glu
 145 150 155 160
 Phe Leu Arg Gln Lys Arg Ser Val Ala Ala Leu Glu Gln Gln Arg Ser
 165 170 175
 Ile Ser Asn Val Asn Asp Asp Ile Asn Thr Gln Asn Met Tyr Thr Lys
 180 185 190
 Arg Gly Ala Asn Glu Lys Trp Ser Leu Arg Lys His Thr Val Ser Leu
 195 200 205
 Ala Thr Asn Ala Phe Gly Gln Val Glu Phe Gln Gly Gly Pro His Pro
 210 215 220
 Tyr Lys Ala Gln Tyr Val Arg Val Asn Phe Asp Thr Glu Pro Ala Tyr
 225 230 235 240
 Ile Met Ser Leu Phe Glu His Val Trp Gln Ile Ser Pro Pro Arg Leu
 245 250 255
 Ile Ile Thr Val His Gly Gly Thr Ser Asn Phe Asp Leu Gln Pro Lys
 260 265 270
 Leu Ala Arg Val Phe Arg Lys Gly Leu Leu Lys Ala Ala Ser Thr Thr
 275 280 285
 Gly Ala Trp Ile Ile Thr Ser Gly Cys Asp Thr Gly Val Val Lys His
 290 295 300
 Val Ala Ala Ala Leu Glu Gly Ala Gln Ser Ala Gln Arg Asn Lys Ile
 305 310 315 320
 Val Cys Ile Gly Ile Ala Pro Trp Gly Leu Leu Lys Lys Arg Glu Asp
 325 330 335
 Phe Ile Gly Gln Asp Lys Thr Val Pro Tyr Tyr Pro Ser Ser Ser Lys
 340 345 350
 Gly Arg Phe Thr Gly Leu Asn Asn Arg His Ser Tyr Phe Leu Leu Val

-26-

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      355      360      365
Asp Asn Gly Thr Val Gly Arg Tyr Gly Ala Glu Val Ile Leu Arg Lys
      370      375      380
Arg Leu Glu Met Tyr Ile Ser Gln Lys Gln Lys Ile Phe Gly Gly Thr
385      390      395      400
Arg Ser Val Pro Val Val Cys Val Val Leu Glu Gly Gly Ser Cys Thr
      405      410      415
Ile Arg Ser Val Leu Asp Tyr Val Thr Asn Val Pro Arg Val Pro Val
      420      425      430
Val Val Cys Asp Gly Ser Gly Arg Ala Ala Asp Leu Leu Ala Phe Ala
      435      440      445
His Gln Asn Val Thr Glu Asp Gly Leu Leu Pro Asp Asp Ile Arg Arg
      450      455      460
Gln Val Leu Leu Leu Val Glu Thr Thr Phe Gly Cys Ser Glu Ala Ala
465      470      475      480
Ala His Arg Leu Leu His Glu Leu Thr Val Cys Ala Gln His Lys Asn
      485      490      495
Leu Leu Thr Ile Phe Arg Leu Gly Glu Gln Gly Glu His Asp Val Asp
      500      505      510
His Ala Ile Leu Thr Ala Leu Leu Lys Gly Gln Asn Leu Ser Ala Ala
      515      520      525
Asp Gln Leu Ala Leu Ala Leu Ala Trp Asn Arg Val Asp Ile Ala Arg
      530      535      540
Ser Asp Val Phe Ala Met Gly His Glu Trp Pro Gln Ala Ala Leu His
545      550      555      560
Asn Ala Met Met Glu Ala Leu Ile His Asp Arg Val Asp Phe Val Arg
      565      570      575
Leu Leu Leu Glu Gln Gly Ile Asn Met Gln Lys Phe Leu Thr Ile Ser
      580      585      590
Arg Leu Asp Glu Leu Tyr Asn Thr Asp Lys Gly Pro Pro Asn Thr Leu
      595      600      605
Phe Tyr Ile Val Arg Asp Val Val Arg Val Arg Gln Gly Tyr Arg Phe
      610      615      620
Lys Leu Pro Asp Ile Gly Leu Val Ile Glu Lys Leu Met Gly Asn Ser
625      630      635      640
Tyr Gln Cys Ser Tyr Thr Thr Ser Glu Phe Arg Asp Lys Tyr Lys Gln
      645      650      655
Arg Met Lys Arg Val Lys His Ala Gln Lys Lys Ala Met Gly Val Phe
      660      665      670
Ser Ser Arg Pro Ser Arg Thr Gly Ser Gly Ile Ala Ser Arg Gln Ser
      675      680      685
Thr Glu Gly Met Gly Gly Val Gly Gly Gly Ser Ser Val Ala Gly Val
      690      695      700
Phe Gly Asn Ser Phe Gly Asn Gln Asp Pro Pro Leu Asp Pro His Val
705      710      715      720
Asn Arg Ser Ala Leu Ser Gly Ser Arg Ala Leu Ser Asn His Ile Leu
      725      730      735
Trp Arg Ser Ala Phe Arg Gly Asn Phe Pro Ala Asn Pro Met Arg Pro
      740      745      750
Pro Asn Leu Gly Asp Ser Arg Asp Cys Gly Ser Glu Phe Asp Glu Glu
      755      760      765
Leu Ser Leu Thr Ser Ala Ser Asp Gly Ser Gln Thr Glu Pro Asp Phe
      770      775      780
Arg Tyr Pro Tyr Ser Glu Leu Met Ile Trp Ala Val Leu Thr Lys Arg
785      790      795      800
Gln Asp Met Ala Met Cys Met Trp Gln His Gly Glu Glu Ala Met Ala
      805      810      815
Lys Ala Leu Val Ala Cys Arg Leu Tyr Lys Ser Leu Ala Thr Glu Ala
      820      825      830
Ala Glu Asp Tyr Leu Glu Val Glu Ile Cys Glu Glu Leu Lys Lys Tyr

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-27-

835	840	845
Ala Glu Glu Phe Arg Ile Leu Ser Leu Glu Leu Leu Asp His Cys Tyr		
850	855	860
His Val Asp Asp Ala Gln Thr Leu Gln Leu Leu Thr Tyr Glu Leu Ser		
865	870	875
Asn Trp Ser Asn Glu Thr Cys Leu Ala Leu Ala Val Ile Val Asn Asn		
885	890	895
Lys His Phe Leu Ala His Pro Cys Cys Gln Ile Leu Leu Ala Asp Leu		
900	905	910
Trp His Gly Gly Leu Arg Met Arg Thr His Ser Asn Ile Lys Val Val		
915	920	925
Leu Gly Leu Ile Cys Pro Pro Phe Ile Gln Met Leu Glu Phe Lys Thr		
930	935	940
Arg Glu Glu Leu Leu Asn Gln Pro Gln Thr Ala Ala Glu His Gln Asn		
945	950	955
Asp Met Asn Tyr Ser Ser Ser Ser Ser Ser Ser Ser Ser Ser Ser		
965	970	975
Ser Ser Ser Ser Ser Asp Ser Ser Ser Phe Glu Asp Asp Asp Asp Glu		
980	985	990
Asn Asn Ala His Asn His Asp Gln Lys Arg Thr Arg Lys Thr Ser Gln		
995	1000	1005
Gly Ser Ala Gln Ser Leu Asn Ile Thr Ser Leu Phe His Ser Arg Arg		
1010	1015	1020
Arg Lys Ala Lys Lys Asn Glu Lys Cys Asp Arg Glu Thr Asp Ala Ser		
1025	1030	1035
Ala Cys Glu Ala Gly Asn Arg Gln Ile Gln Asn Gly Gly Leu Thr Ala		
1045	1050	1055
Glu Tyr Gly Thr Phe Gly Glu Ser Asn Gly Val Ser Pro Pro Pro Pro		
1060	1065	1070
Tyr Met Arg Ala Asn Ser Arg Ser Arg Tyr Asn Asn Arg Ser Asp Met		
1075	1080	1085
Ser Lys Thr Ser Ser Val Ile Phe Gly Ser Asp Pro Asn Leu Ser Lys		
1090	1095	1100
Leu Gln Lys Ser Asn Ile Thr Ser Thr Asp Arg Pro Asn Pro Met Glu		
1105	1110	1115
Gln Phe Gln Gly Thr Arg Lys Ile Lys Met Arg Arg Arg Phe Tyr Glu		
1125	1130	1135
Phe Tyr Ser Ala Pro Ile Ser Thr Phe Trp Ser Trp Thr Ile Ser Phe		
1140	1145	1150
Ile Leu Phe Ile Thr Phe Phe Thr Tyr Thr Leu Leu Val Lys Thr Pro		
1155	1160	1165
Pro Arg Pro Thr Val Ile Glu Tyr Ile Leu Ile Ala Tyr Val Ala Ala		
1170	1175	1180
Phe Gly Leu Glu Gln Val Arg Lys Ile Ile Met Ser Asp Ala Lys Pro		
1185	1190	1195
Phe Tyr Glu Lys Ile Arg Thr Tyr Val Cys Ser Phe Trp Asn Cys Val		
1205	1210	1215
Thr Ile Leu Ala Ile Ile Phe Tyr Ile Val Gly Phe Phe Met Arg Cys		
1220	1225	1230
Phe Gly Ser Val Ala Tyr Gly Arg Val Ile Leu Ala Cys Asp Ser Val		
1235	1240	1245
Leu Trp Thr Met Lys Leu Leu Asp Tyr Met Ser Val His Pro Lys Leu		
1250	1255	1260
Gly Pro Tyr Val Thr Met Ala Gly Lys Met Ile Gln Asn Met Ser Tyr		
1265	1270	1275
Ile Ile Val Met Leu Val Val Thr Leu Leu Ser Phe Gly Leu Ala Arg		
1285	1290	1295
Gln Ser Ile Thr Tyr Pro Asp Glu Thr Trp His Trp Ile Leu Val Arg		
1300	1305	1310
Asn Ile Phe Leu Lys Pro Tyr Phe Met Leu Tyr Gly Glu Val Tyr Ala		

-28-

1315 1320 1325
 Asp Glu Ile Asp Thr Cys Gly Asp Glu Ala Trp Asp Gln His Leu Glu
 1330 1335 1340
 Asn Gly Gly Pro Val Ile Leu Gly Asn Gly Thr Thr Gly Leu Ser Cys
 1345 1350 1355 136
 Val Pro Gly Tyr Trp Ile Pro Pro Leu Leu Met Thr Phe Phe Leu Leu
 1365 1370 1375
 Ile Ala Asn Ile Leu Leu Met Ser Met Leu Ile Ala Ile Phe Asn His
 1380 1385 1390
 Ile Phe Asp Ala Thr Asp Glu Met Ser Gln Gln Ile Trp Leu Phe Gln
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 Arg Tyr Lys Gln Val Met Glu Tyr Glu Ser Thr Pro Phe Leu Pro Pro
 1410 1415 1420
 Pro Leu Thr Pro Leu Tyr His Gly Val Leu Ile Leu Gln Phe Val Arg
 1425 1430 1435 144
 Thr Arg Leu Ser Cys Ser Lys Ser Gln Glu Arg Asn Pro Ile Leu Leu
 1445 1450 1455
 Leu Lys Ile Ala Glu Leu Phe Leu Asp Asn Asp Gln Ile Glu Lys Leu
 1460 1465 1470
 His Asp Phe Glu Glu Asp Cys Met Glu Asp Leu Ala Arg Gln Lys Leu
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 Asn Glu Lys Asn Thr Ser Asn Glu Gln Arg Ile Leu Arg Ala Asp Ile
 1490 1495 1500
 Arg Thr Asp Gln Ile Leu Asn Arg Leu Ile Asp Leu Gln Ala Lys Glu
 1505 1510 1515 152
 Ser Met Gly Arg Asp Val Ile Asn Asp Val Glu Ser Arg Leu Ala Ser
 1525 1530 1535
 Val Glu Lys Ala Gln Asn Glu Ile Leu Glu Cys Val Arg Ala Leu Leu
 1540 1545 1550
 Asn Gln Asn Asn Ala Pro Thr Ala Ile Gly Arg Cys Phe Ser Pro Ser
 1555 1560 1565
 Pro Asp Pro Leu Val Glu Thr Ala Asn Gly Thr Pro Gly Pro Leu Leu
 1570 1575 1580
 Leu Lys Leu Pro Gly Thr Asp Pro Ile Leu Glu Glu Lys Asp His Asp
 1585 1590 1595 160
 Ser Gly Glu Asn Ser Asn Ser Leu Pro Pro Gly Arg Ile Arg Arg Asn
 1605 1610 1615
 Arg Thr Ala Thr Ile Cys Gly Gly Tyr Val Ser Glu Glu Arg Asn Met
 1620 1625 1630
 Met Leu Leu Ser Pro Lys Pro Ser Asp Val Ser Gly Ile Pro Gln Gln
 1635 1640 1645
 Arg Leu Met Ser Val Thr Ser Met Asp Pro Leu Pro Leu Pro Leu Ala
 1650 1655 1660
 Lys Leu Ser Thr Met Ser Ile Arg Arg Arg His Glu Glu Tyr Thr Ser
 1665 1670 1675 168
 Ile Thr Asp Ser Ile Ala Ile Arg His Pro Glu Arg Arg Ile Arg Asn
 1685 1690 1695
 Asn Arg Ser Asn Ser Ser Glu His Asp Glu Ser Ala Val Asp Ser Glu
 1700 1705 1710
 Gly Gly Gly Asn Val Thr Ser Ser Pro Arg Lys Arg Ser Thr Arg Asp
 1715 1720 1725
 Leu Arg Met Thr Pro Ser Ser Gln Val Glu Glu Ser Thr Ser Arg Asp
 1730 1735 1740
 Gln Ile Phe Glu Ile Asp His Pro Glu His Glu Glu Asp Glu Ala Gln
 1745 1750 1755 176
 Ala Asp Cys Glu Leu Thr Asp Val Ile Thr Glu Glu Glu Asp Glu Glu
 1765 1770 1775
 Glu Asp Asp Glu Glu Asp Asp Ser His Glu Arg His His Ile His Pro
 1780 1785 1790
 Arg Arg Lys Ser Ser Arg Gln Asn Arg Gln Pro Ser His Thr Leu Glu

-29-

1795 1800 1805
 Thr Asp Leu Ser Glu Gly Glu Glu Val Asp Pro Leu Asp Val Leu Lys
 1810 1815 1820
 Met Lys Glu Leu Pro Ile Ile His Gln Ile Leu Asn Glu Glu Glu Gln
 1825 1830 1835 184
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 1845 1850 1855
 Arg Ala Asp Leu Thr Ser Gln Lys Cys Ser Asp Val
 1860 1865

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 <211> 489
 <212> DNA
 <213> Mus Musculus

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 ggctgcaggc cgcgagggtg gaggaggagc cgctgccctt ccggagtccg ccccgtaggg 180
 agaatgtccc agaaatcctg gatagagagc actttgacca agagggagtg tgtatatatt 240
 ataccaagct ccaaagacc cccacagatgt cttccaggat gtcagatttg tcagcaactt 300
 gtcagatgtt tctgtggtcg tttggtcaag caacatgcat gctttactgc aagtcttgcc 360
 atgaaatact cagatgtgaa attgggtgaa cactttaacc aggcaataga agaatggtct 420
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 ggttctcat 489

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 <211> 102
 <212> PRT
 <213> Mus Musculus

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 Val Tyr Ile Ile Pro Ser Ser Lys Asp Pro His Arg Cys Leu Pro Gly
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 Cys Gln Ile Cys Gln Gln Leu Val Arg Cys Phe Cys Gly Arg Leu Val
 35 40 45
 Lys Gln His Ala Cys Phe Thr Ala Ser Leu Ala Met Lys Tyr Ser Asp
 50 55 60
 Val Lys Leu Gly Glu His Phe Asn Gln Ala Ile Glu Glu Trp Ser Val
 65 70 75 80
 Glu Lys His Thr Glu Gln Ser Pro Thr Asp Ala Tyr Gly Val Ile Asn
 85 90 95
 Phe Gln Gly Gly Ser His
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<210> 18
 <211> 410
 <212> DNA
 <213> Homo Sapiens

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 <221> unsure
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<221> unsure

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<222> (406)...(406)

<400> 18

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ctagtggctc	tcacctgctt	cctcctgggc	gtgggctgcc	ggctgacccc	gggtttgtac	180
cacctgggcc	gcaactgtct	ctgcatcgac	ttcatgggtt	tcacgggtgcg	gctgcttcac	240
atcttcacgg	tcaacaaaca	gctggggccc	aagatcgcca	tcgtgagcaa	gatgatgaag	300
gacgtgttct	tcttcctctt	cttcctcggc	gtgtggctgg	tagctatggg	ttggggccacg	360
gaggggttcc	tgaggccacg	ggacagtgac	ttcccaagta	tcctgncgcc		410

<210> 19

<211> 131

<212> PRT

<213> Homo Sapiens

<220>

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<223> UNKNOWN

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<223> UNKNOWN

<400> 19

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-31-

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-34-

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-35-

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-36-

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-37-

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-38-

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-42-

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Gly	Leu	Val	Ile	Glu	Tyr	Leu	Met	Gly	Gly	Thr	Tyr	Arg	Cys	Thr	Tyr
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Thr	Arg	Lys	Arg	Phe	Arg	Leu	Ile	Tyr	Asn	Ser	Leu	Gly	Gly	Asn	Asn
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Arg	Arg	Ser	Gly	Arg	Asn	Thr	Ser	Ser	Ser	Thr	Pro	Gln	Leu	Arg	Lys
545					550					555					560
Ser	His	Glu	Ser	Phe	Gly	Asn	Arg	Ala	Asp	Lys	Lys	Glu	Lys	Met	Arg
				565					570					575	
His	Asn	His	Phe	Ile	Lys	Thr	Ala	Gln	Pro	Phe	Arg	Pro	Lys	Ile	Asp
			580					585					590		
Thr	Val	Met	Glu	Glu	Gly	Lys	Lys	Arg	Thr	Lys	Asp	Glu	Ile	Val	
			595				600				605				
Asp	Ile	Asp	Asp	Pro	Glu	Thr	Lys	Arg	Phe	Pro	Tyr	Pro	Leu	Asn	Glu
					610		615				620				
Leu	Leu	Ile	Trp	Ala	Cys	Leu	Met	Lys	Arg	Gln	Val	Met	Ala	Arg	Phe
625					630					635					640
Leu	Trp	Gln	His	Gly	Glu	Glu	Ser	Met	Ala	Lys	Ala	Leu	Val	Ala	Cys
				645					650					655	
Lys	Ile	Tyr	Arg	Ser	Met	Ala	Tyr	Glu	Ala	Lys	Gln	Ser	Asp	Leu	Val
			660					665					670		
Asp	Asp	Thr	Ser	Glu	Glu	Leu	Lys	Gln	Tyr	Ser	Asn	Asp	Phe	Gly	Gln
			675				680					685			
Leu	Ala	Val	Glu	Leu	Leu	Glu	Gln	Ser	Phe	Arg	Gln	Asp	Glu	Thr	Met
			690			695					700				
Ala	Met	Lys	Leu	Leu	Thr	Tyr	Glu	Leu	Lys	Asn	Trp	Ser	Asn	Ser	Thr
705					710					715					720
Cys	Leu	Lys	Leu	Ala	Val	Ser	Ser	Arg	Leu	Arg	Pro	Phe	Val	Ala	His
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Thr	Cys	Thr	Gln	Met	Leu	Leu	Ser	Asp	Met	Trp	Met	Gly	Arg	Leu	Asn
			740					745					750		
Met	Arg	Lys	Asn	Ser	Trp	Tyr	Lys	Val	Ile	Leu	Ser	Ile	Leu	Val	Pro
		755					760					765			
Pro	Ala	Ile	Leu	Leu	Leu	Glu	Tyr	Lys	Thr	Lys	Ala	Glu	Met	Ser	His
		770				775						780			
Ile	Pro	Gln	Ser	Gln	Asp	Ala	His	Gln	Met	Thr	Met	Asp	Asp	Ser	Glu
785					790					795					800
Asn	Asn	Phe	Gln	Asn	Ile	Thr	Glu	Glu	Ile	Pro	Met	Glu	Val	Phe	Lys
				805					810					815	
Glu	Val	Arg	Ile	Leu	Asp	Ser	Asn	Glu	Gly	Lys	Asn	Glu	Met	Glu	Ile
			820					825					830		
Gln	Met	Lys	Ser	Lys	Lys	Leu	Pro	Ile	Thr	Arg	Lys	Phe	Tyr	Ala	Phe
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-43-

Tyr His Ala Pro Ile Val Lys Phe Trp Phe Asn Thr Leu Ala Tyr Leu
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 Gly Phe Leu Met Leu Tyr Thr Phe Val Val Leu Val Gln Met Glu Gln
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 Leu Pro Ser Val Gln Glu Trp Ile Val Ile Ala Tyr Ile Phe Thr Tyr
 885 890 895
 Ala Ile Glu Lys Val Arg Glu Ile Phe Met Ser Glu Ala Gly Lys Val
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 Asn Gln Lys Ile Lys Val Trp Phe Ser Asp Tyr Phe Asn Ile Ser Asp
 915 920 925
 Thr Ile Ala Ile Ile Ser Phe Phe Ile Gly Phe Gly Leu Arg Phe Gly
 930 935 940
 Ala Lys Trp Asn Phe Ala Asn Ala Tyr Asp Asn His Val Phe Val Ala
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 Gly Arg Leu Ile Tyr Cys Leu Asn Ile Ile Phe Trp Tyr Val Arg Leu
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 Leu Asp Phe Leu Ala Val Asn Gln Gln Ala Gly Pro Tyr Val Met Met
 980 985 990
 Ile Gly Lys Met Val Ala Asn Met Phe Tyr Ile Val Val Ile Met Ala
 995 1000 1005
 Leu Val Leu Leu Ser Phe Gly Val Pro Arg Lys Ala Ile Leu Tyr Pro
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 His Glu Ala Pro Ser Trp Thr Leu Ala Lys Asp Ile Val Phe His Pro
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 Tyr Trp Met Ile Phe Gly Glu Val Tyr Ala Tyr Glu Ile Asp Val Cys
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 Ala Asn Asp Ser Val Ile Pro Gln Ile Cys Gly Pro Gly Thr Trp Leu
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 Thr Pro Phe Leu Gln Ala Val Tyr Leu Phe Val Gln Tyr Ile Ile Met
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 Val Asn Leu Leu Ile Ala Phe Phe Asn Asn Val Tyr Leu Gln Val Lys
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 Ala Ile Ser Asn Ile Val Trp Lys Tyr Gln Arg Tyr His Phe Ile Met
 1105 1110 1115 1120
 Ala Tyr His Glu Lys Pro Val Leu Pro Pro Pro Leu Ile Ile Leu Ser
 1125 1130 1135
 His Ile Val Ser Leu Phe Cys Cys Ile Cys Lys Arg Arg Lys Lys Asp
 1140 1145 1150
 Lys Thr Ser Asp Gly Pro Lys Leu Phe Leu Thr Glu Glu Asp Gln Lys
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 Lys Leu His Asp Phe Glu Glu Gln Cys Val Glu Met Tyr Phe Asn Glu
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 Lys Asp Asp Lys Phe His Ser Gly Ser Glu Glu Arg Ile Arg Val Thr
 1185 1190 1195 1200
 Phe Glu Arg Val Glu Gln Met Cys Ile Gln Ile Lys Glu Val Gly Asp
 1205 1210 1215
 Arg Val Asn Tyr Ile Lys Arg Ser Leu Gln Ser Leu Asp Ser Gln Ile
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 Gly His Leu Gln Asp Leu Ser Ala Leu Thr Val Asp Thr Leu Lys Thr
 1235 1240 1245
 Leu Thr Ala Gln Lys Ala Ser Glu Ala Ser Lys Val His Asn Glu Ile
 1250 1255 1260
 Thr Arg Glu Leu Ser Ile Ser Lys His Leu Ala Gln Asn Leu Ile Asp
 1265 1270 1275 1280
 Asp Gly Pro Val Arg Pro Ser Val Trp Lys Lys His Gly Val Val Asn
 1285 1290 1295
 Thr Leu Ser Ser Ser Leu Pro Gln Gly Asp Leu Glu Ser Asn Asn Pro
 1300 1305 1310
 Phe His Cys Asn Ile Leu Met Lys Asp Asp Lys Asp Pro Gln Cys Asn
 1315 1320 1325

-44-

Ile Phe Gly Gln Asp Leu Pro Ala Val Pro Gln Arg Lys Glu Phe Asn
 1330 1335 1340
 Phe Pro Glu Ala Gly Ser Ser Gly Ala Leu Phe Pro Ser Ala Val
 1345 1350 1355 1360
 Ser Pro Pro Glu Leu Arg Gln Arg Leu His Gly Val Glu Leu Leu Lys
 1365 1370 1375
 Ile Phe Asn Lys Asn Gln Lys Leu Gly Ser Ser Ser Thr Ser Ile Pro
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 His Leu Ser Ser Pro Pro Thr Lys Phe Phe Val Ser Thr Pro Ser Gln
 1395 1400 1405
 Pro Ser Cys Lys Ser His Leu Glu Thr Gly Thr Lys Asp Gln Glu Thr
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 Val Cys Ser Lys Ala Thr Glu Gly Asp Asn Thr Glu Phe Gly Ala Phe
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 Val Gly His Arg Asp Ser Met Asp Leu Gln Arg Phe Lys Glu Thr Ser
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 Asn Lys Ile Lys Ile Leu Ser Asn Asn Asn Thr Ser Glu Asn Thr Leu
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 Lys Arg Val Ser Ser Leu Ala Gly Phe Thr Asp Cys His Arg Thr Ser
 1475 1480 1485
 Ile Pro Val His Ser Lys Gln Ala Glu Lys Ile Ser Arg Arg Pro Ser
 1490 1495 1500
 Thr Glu Asp Thr His Glu Val Asp Ser Lys Ala Ala Leu Ile Pro Asp
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 Trp Leu Gln Asp Arg Pro Ser Asn Arg Glu Met Pro Ser Glu Glu Gly
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 Thr Leu Asn Gly Leu Thr Ser Pro Phe Lys Pro Ala Met Asp Thr Asn
 1540 1545 1550
 Tyr Tyr Tyr Ser Ala Val Glu Arg Asn Asn Leu Met Arg Leu Ser Gln
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 Ser Ile Pro Phe Thr Pro Val Pro Pro Arg Gly Glu Pro Val Thr Val
 1570 1575 1580
 Tyr Arg Leu Glu Glu Ser Ser Pro Asn Ile Leu Asn Asn Ser Met Ser
 1585 1590 1595 1600
 Ser Trp Ser Gln Leu Gly Leu Cys Ala Lys Ile Glu Phe Leu Ser Lys
 1605 1610 1615
 Glu Glu Met Gly Gly Gly Leu Arg Arg Ala Val Lys Val Gln Cys Thr
 1620 1625 1630
 Trp Ser Glu His Asp Ile Leu Lys Ser Gly His Leu Tyr Ile Ile Lys
 1635 1640 1645
 Ser Phe Leu Pro Glu Val Val Asn Thr Trp Ser Ser Ile Tyr Lys Glu
 1650 1655 1660
 Asp Thr Val Leu His Leu Cys Leu Arg Glu Ile Gln Gln Gln Arg Ala
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 Ala Gln Lys Leu Thr Phe Ala Phe Asn Gln Met Lys Pro Lys Ser Ile
 1685 1690 1695
 Pro Tyr Ser Pro Arg Phe Leu Glu Val Phe Leu Leu Tyr Cys His Ser
 1700 1705 1710
 Ala Gly Gln Trp Phe Ala Val Glu Glu Cys Met Thr Gly Glu Phe Arg
 1715 1720 1725
 Lys Tyr Asn Asn Asn Asn Gly Asp Glu Ile Ile Pro Thr Asn Thr Leu
 1730 1735 1740
 Glu Glu Ile Met Leu Ala Phe Ser His Trp Thr Tyr Glu Tyr Thr Arg
 1745 1750 1755 1760
 Gly Glu Leu Leu Val Leu Asp Leu Gln Gly Val Gly Glu Asn Leu Thr
 1765 1770 1775
 Asp Pro Ser Val Ile Lys Ala Glu Glu Lys Arg Ser Cys Asp Met Val
 1780 1785 1790
 Phe Gly Pro Ala Asn Leu Gly Glu Asp Ala Ile Lys Asn Phe Arg Ala
 1795 1800 1805

-45-

Lys His His Cys Asn Ser Cys Cys Arg Lys Leu Lys Leu Pro Asp Leu
 1810 1815 1820
 Lys Arg Asn Asp Tyr Thr Pro Asp Lys Ile Ile Phe Pro Gln Asp Glu
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 Ser Thr Asn Ser Val Arg Leu Met Leu
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 aagaagacct gcacgacgtt catagttgac tccacagatc cgggagggac cttgtgccag 180
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-46-

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<211> 1214

<212> PRT

<213> Homo Sapiens

<400> 30

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Thr Leu Cys Gln Cys Gly Arg Pro Arg Thr Ala His Pro Ala Val Ala
35      40      45
Met Glu Asp Ala Phe Gly Ala Ala Val Val Thr Val Trp Asp Ser Asp
50      55      60
Ala His Thr Thr Glu Lys Pro Thr Asp Ala Tyr Gly Glu Leu Asp Phe
65      70      75      80
Thr Gly Ala Gly Arg Lys His Ser Asn Phe Leu Arg Leu Ser Asp Arg
85      90      95
Thr Asp Pro Ala Ala Val Tyr Ser Leu Val Thr Arg Thr Trp Gly Phe
100     105     110
Arg Ala Pro Asn Leu Val Val Ser Val Leu Gly Gly Ser Gly Gly Pro
115     120     125
Val Leu Gln Thr Trp Leu Gln Asp Leu Leu Arg Arg Gly Leu Val Arg
130     135     140
Ala Ala Gln Ser Thr Gly Ala Trp Ile Val Thr Gly Gly Leu His Thr
145     150     155     160
Gly Ile Gly Arg His Val Gly Val Ala Val Arg Asp His Gln Met Ala
165     170     175
Ser Thr Gly Gly Thr Lys Val Val Ala Met Gly Val Ala Pro Trp Gly
180     185     190
Val Val Arg Asn Arg Asp Thr Leu Ile Asn Pro Lys Gly Ser Phe Pro
195     200     205
Ala Arg Tyr Arg Trp Arg Gly Asp Pro Glu Asp Gly Val Gln Phe Pro
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Leu Asp Tyr Asn Tyr Ser Ala Phe Phe Leu Val Asp Asp Gly Thr His
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Ile	Ser	Gln	Gln 260	Lys	Thr	Gly	Val	Gly 265	Gly	Thr	Gly	Ile	Asp	Ile	Pro
Val	Leu	Leu 275	Leu	Leu	Ile	Asp	Gly 280	Asp	Glu	Lys	Met	Leu	Thr	Arg	Ile
Glu 290	Asn	Ala	Thr	Gln	Ala	Gln 295	Leu	Pro	Cys	Leu	Leu 300	Val	Ala	Gly	Ser
Gly 305	Gly	Ala	Ala	Asp	Cys	Leu	Ala	Glu	Thr	Leu	Glu 315	Asp	Thr	Leu	Ala
Pro	Gly	Ser	Gly	Gly 325	Ala	Arg	Gln	Gly	Glu	Ala	Arg	Asp	Arg	Ile	Arg
Arg	Phe	Phe	Pro 340	Lys	Gly	Asp	Leu	Glu 345	Val	Leu	Gln	Ala	Gln	Val	Glu
Arg	Ile	Met 355	Thr	Arg	Lys	Glu	Leu	Leu 360	Thr	Val	Tyr	Ser	Ser	Glu	Asp
Gly	Ser	Glu	Glu	Phe	Glu	Thr 375	Ile	Val	Leu	Lys	Ala	Leu	Val	Lys	Ala
Cys 385	Gly	Ser	Ser	Glu	Ala	Ser	Ala	Tyr	Leu	Asp	Glu	Leu	Arg	Leu	Ala
Val	Ala	Trp	Asn	Arg 405	Val	Asp	Ile	Ala	Gln	Ser	Glu	Leu	Phe	Arg	Gly
Asp	Ile	Gln	Trp	Arg	Ser	Phe	His	Leu 425	Glu	Ala	Ser	Leu	Met	Asp	Ala
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Leu	Ser	Leu	Gly	His	Phe	Leu 455	Thr	Pro	Met	Arg	Leu	Ala	Gln	Leu	Tyr
Ser	Ala	Ala	Pro	Ser	Asn	Ser	Leu	Ile	Arg	Asn	Leu	Leu	Asp	Gln	Ala
Ser	His	Ser	Ala	Gly 485	Thr	Lys	Ala	Pro	Ala	Leu	Lys	Gly	Gly	Ala	Ala
Glu	Leu	Arg	Pro	Pro	Asp	Val	Gly	His 505	Val	Leu	Arg	Met	Leu	Leu	Gly
Lys	Met	Cys 515	Ala	Pro	Arg	Tyr	Pro	Ser	Gly	Gly	Ala	Trp	Asp	Pro	His
Pro	Gly	Gln	Gly	Phe	Gly	Glu	Ser	Met	Tyr	Leu	Leu	Ser	Asp	Lys	Ala
Thr 545	Ser	Pro	Leu	Ser	Leu	Asp	Ala	Gly	Leu	Gly	Gln	Ala	Pro	Trp	Ser
Asp	Leu	Leu	Leu	Trp	Ala	Leu	Leu	Leu	Asn	Arg	Ala	Gln	Met	Ala	Met
Tyr	Phe	Trp	Glu	Met	Gly	Ser	Asn	Ala	Val	Ser	Ser	Ala	Leu	Gly	Ala
Cys	Leu	Leu	Leu	Arg	Val	Met	Ala	Arg	Leu	Glu	Pro	Asp	Ala	Glu	Glu
Ala	Ala	Arg	Arg	Lys	Asp	Leu	Ala	Phe	Lys	Phe	Glu	Gly	Met	Gly	Val
Asp 625	Leu	Phe	Gly	Glu	Cys	Tyr	Arg	Ser	Ser	Glu	Val	Arg	Ala	Ala	Arg
Leu	Leu	Leu	Arg	Arg	Cys	Pro	Leu	Trp	Gly	Asp	Ala	Thr	Cys	Leu	Gln
Leu	Ala	Met	Gln	Ala	Asp	Ala	Arg	Ala	Phe	Phe	Ala	Gln	Asp	Gly	Val
Gln	Ser	Leu	Leu	Thr	Gln	Lys	Trp	Trp	Gly	Asp	Met	Ala	Ser	Thr	Thr
Pro	Ile	Trp	Ala	Leu	Val	Leu	Ala	Phe	Phe	Cys	Pro	Pro	Leu	Ile	Tyr
Thr 705	Arg	Leu	Ile	Thr	Phe	Arg	Lys	Ser	Glu	Glu	Glu	Pro	Thr	Arg	Glu

-48-

Glu Leu Glu Phe Asp Met Asp Ser Val Ile Asn Gly Glu Gly Pro Val
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 Gly Thr Ala Asp Pro Ala Glu Lys Thr Pro Leu Gly Val Pro Arg Gln
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 755 760 765
 Leu Arg Arg Trp Phe His Phe Trp Gly Ala Pro Val Thr Ile Phe Met
 770 775 780
 Gly Asn Val Val Ser Tyr Leu Leu Phe Leu Leu Phe Ser Arg Val
 785 790 795 800
 Leu Leu Val Asp Phe Gln Pro Ala Pro Pro Gly Ser Leu Glu Leu Leu
 805 810 815
 Leu Tyr Phe Trp Ala Phe Thr Leu Leu Cys Glu Glu Leu Arg Gln Gly
 820 825 830
 Leu Ser Gly Gly Gly Ser Leu Ala Ser Gly Gly Pro Gly Pro Gly
 835 840 845
 His Ala Ser Leu Ser Gln Arg Leu Arg Leu Tyr Leu Ala Asp Ser Trp
 850 855 860
 Asn Gln Cys Asp Leu Val Ala Leu Thr Cys Phe Leu Leu Gly Val Gly
 865 870 875 880
 Cys Arg Leu Thr Pro Gly Leu Tyr His Leu Gly Arg Thr Val Leu Cys
 885 890 895
 Ile Asp Phe Met Val Phe Thr Val Arg Leu Leu His Ile Phe Thr Val
 900 905 910
 Asn Lys Gln Leu Gly Pro Lys Ile Val Ile Val Ser Lys Met Met Lys
 915 920 925
 Asp Val Phe Phe Phe Leu Phe Phe Leu Gly Val Trp Leu Val Ala Tyr
 930 935 940
 Gly Val Ala Thr Glu Gly Leu Leu Arg Pro Arg Asp Ser Asp Phe Pro
 945 950 955 960
 Ser Ile Leu Arg Arg Val Phe Tyr Arg Pro Tyr Leu Gln Ile Phe Gly
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 Gln Ile Pro Gln Glu Asp Met Asp Val Ala Leu Met Glu His Ser Asn
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 Cys Ser Ser Glu Pro Gly Phe Trp Ala His Pro Pro Gly Ala Gln Ala
 995 1000 1005
 Gly Thr Cys Val Ser Gln Tyr Ala Asn Trp Leu Val Val Leu Leu Leu
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-52-

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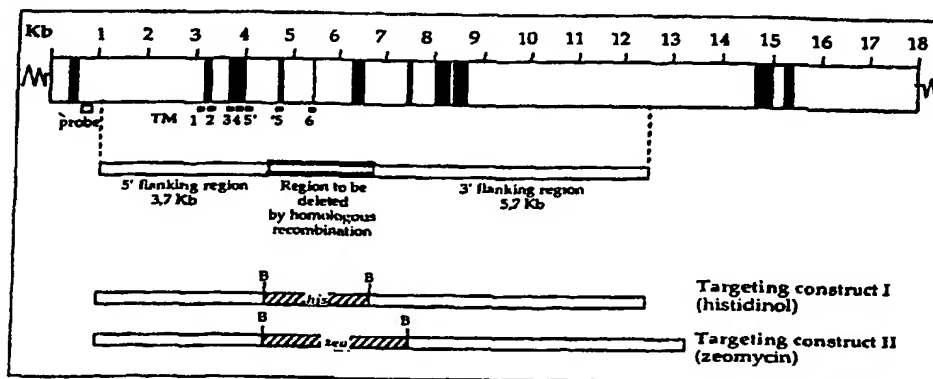
(15) Information about Correction:
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(72) Inventor; and

(75) Inventor/Applicant (*for US only*): SCHARENBERG,
Andrew, M. [US/US]; 12 Skyview Road, Lexington, MA
02420 (US).

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: CHARACTERIZATION OF THE SOC/CRAC CALCIUM CHANNEL PROTEIN FAMILY



(57) Abstract: Nucleic acids encoding SOC/CRAC calcium channel polypeptides, including fragments and biologically functional variants thereof and encoded polypeptides are provided. The nucleic acids and polypeptides disclosed herein are useful as therapeutic and diagnostic agents. Agents that selectively bind to the foregoing polypeptides and genes also are provided.

CHARACTERIZATION OF A CALCIUM CHANNEL FAMILY

Field of the Invention

This invention relates to nucleic acids coding for a novel family of calcium channel polypeptides, the encoded polypeptides, unique fragments of the foregoing, and methods of making and using same.

Background of the Invention

Calcium channels are membrane-spanning, multi-subunit proteins that facilitate the controlled transport ("flux") of Ca^{2+} ions into and out of cells. Cells throughout the animal kingdom, and at least some bacterial, fungal and plant cells, possess one or more types of calcium channels. In general, "excitable" cells, such as neurons of the central nervous system, peripheral nerve cells, and muscle cells, including those of skeletal muscles, cardiac muscles, and venous and arterial smooth muscles, possess voltage-dependent calcium channels. In a voltage-dependent calcium channel, the transport of Ca^{2+} ions into and out of the cells requires a certain minimal level of depolarization (the difference in potential between the inside of the cell bearing the channel and the extracellular environment) with the rate of Ca^{2+} cell flux dependent on the difference in potential. In "non-excitable" cells, calcium influx is thought to occur predominantly in response to stimuli which cause the release of calcium from intracellular stores. This process, termed *store operated calcium influx*, is not well understood.

Characterization of a particular type of calcium channel by analysis of whole cells is complicated by the presence of mixed populations of different types of calcium channels in the majority of cells. Although single-channel recording methods can be used to examine individual calcium channels, such analysis does not reveal information related to the molecular structure or biochemical composition of the channel. Furthermore, in this type of analysis, the channel is isolated from other cellular constituents that might be important for the channel's natural functions and pharmacological interactions. To study the calcium channel structure-function relationship, large amounts of pure channel protein are needed. However, acquiring large amounts of pure protein is difficult in view of the complex nature of these multisubunit proteins, the varying concentrations of calcium channel proteins in tissue sources, the presence of mixed populations of calcium channel proteins in tissues, and the modifications of the native protein that can occur during the isolation procedure.

Summary of the Invention

The invention is based on the identification of a novel family of calcium channel polypeptides and the molecular cloning and partial characterization of a novel member of this family that is expressed predominantly in human hematopoietic cells, liver, and kidney. This newly identified family of calcium channel polypeptides is designated, "SOC" or "CRAC" or "ICRAC", for Store Operated Channels or Calcium Release Activated Channels. Although not wishing to be bound to any particular theory or mechanism, it is believed that the SOC/CRAC calcium channel polypeptides are transmembrane polypeptides that modulate Ca^{2+} flux "into" and "out of" a cell, for example, in certain instances they may be activated upon depletion of Ca^{2+} from intracellular calcium stores, allowing Ca^{2+} influx into the cell. Accordingly, the compositions disclosed herein are believed to be useful for modulating calcium transport into and out of such intracellular stores and for the treatment of disorders that are characterized by aberrant calcium transport into and out of such intracellular stores. In particular, we believe that the SOC/CRAC calcium channel polypeptides disclosed herein play an important role in the influx of extracellular calcium by mediating the refilling of intracellular calcium stores following their depletion. Accordingly, we believe that the compositions for expressing functional SOC/CRAC calcium channel polypeptides in cells, as disclosed herein, are useful for treating patients having conditions that are characterized by reduced extracellular calcium influx into their SOC/CRAC-expressing cells. Additionally, the compositions of the invention are useful for delivering therapeutic and/or imaging agents to cells which preferentially express SOC/CRAC calcium channel polypeptides and, in particular, for delivering such agents to hematopoietic cells, liver, heart, spleen, and kidney to modulate proliferation and growth of these cells. Moreover, in view of the importance of cellular calcium levels to cell viability, we believe that SOC-2/CRAC-1, SOC-3/CRAC-2, and SOC-4/CRAC-3 as disclosed herein, and/or other members of the SOC/CRAC family of calcium channel polypeptides, represent an ideal target for designing and/or identifying (e.g., from molecular libraries) small molecule inhibitors that block lymphocyte proliferation, as well as other binding agents that selectively bind to SOC/CRAC polypeptides to which drugs or toxins can be conjugated for delivery to SOC/CRAC polypeptide expressing cells.

The invention is based, in part, on the molecular cloning and sequence analysis of the novel SOC/CRAC calcium channel molecules disclosed herein (also referred to as a "SOC-2/CRAC-1 molecule," a "SOC-3/CRAC-2 molecule," and/or "SOC-4/CRAC-3 molecule") that are predominantly expressed in human hematopoietic cells, liver, spleen, heart, and

kidney (SOC-2/CRAC-1), kidney and colon (SOC-3/CRAC-2), and prostate (SOC-4/CRAC-3 molecule). As used herein, a "SOC/CRAC molecule" embraces a "SOC/CRAC calcium channel nucleic acid" (or "SOC/CRAC nucleic acid") and a "SOC/CRAC calcium channel polypeptide" (or "SOC/CRAC polypeptide"). Homologs and alleles also are embraced within
5 the meaning of a SOC/CRAC calcium channel molecule.

According to one aspect of the invention, isolated SOC/CRAC nucleic acids which code for one or more member(s) of the SOC/CRAC family of calcium channel polypeptides or unique fragments thereof are provided. The isolated nucleic acids refer to one or more of the following:

10 (a) nucleic acid molecules which hybridize under stringent conditions to a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, and which code for a SOC/CRAC polypeptide;

15 (b) deletions, additions and substitutions of (a) which code for a respective SOC/CRAC polypeptide;

(c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) in codon sequence due to the degeneracy of the genetic code, and

(d) complements of (a), (b) or (c).

The invention in another aspect provides an isolated nucleic acid molecule selected
20 from the group consisting of (a) a unique fragment of a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:29, and SEQ ID NO:31, (b) complements of (a), provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to any sequence selected from a sequence group consisting of (1) sequences having
25 the SEQ. ID NOS. or GenBank accession numbers of Table I, (2) complements of (1), and (3) fragments of (1) and (2).

According to yet another aspect of the invention, isolated SOC/CRAC polypeptides are provided. The isolated SOC/CRAC polypeptide molecules are encoded by one or more SOC/CRAC nucleic acid molecules of the invention. Preferably, the SOC/CRAC polypeptide
30 contains one or more polypeptides selected from the group consisting of the polypeptides having SEQ. ID Nos. 2, 4, 6, 8, 24, 26, 28, 30, and 32. In other embodiments, the isolated polypeptide may be a fragment or variant of the foregoing SOC/CRAC polypeptide molecules of sufficient length to represent a sequence unique within the human genome, and identifying

with a polypeptide that functions as a calcium channel, provided that the fragment excludes a sequence of contiguous amino acids identified in Table II. and/or excludes a sequence of contiguous amino acids encoded for by a nucleic acid sequence identified in Table I. In another embodiment, immunogenic fragments of the polypeptide molecules described above are provided.

According to another aspect of the invention, isolated SOC/CRAC binding agents (e.g., polypeptides) are provided which selectively bind to a SOC/CRAC molecule (e.g., a SOC/CRAC polypeptide encoded by the isolated nucleic acid molecules of the invention). Preferably, the isolated binding agents selectively bind to a polypeptide which comprises the sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32, or unique fragments thereof. In the preferred embodiments, the isolated binding polypeptides include antibodies and fragments of antibodies (e.g., Fab, F(ab)₂, Fd and antibody fragments which include a CDR3 region which binds selectively to a SOC/CRAC polypeptide). Preferably, the antibodies for human therapeutic applications are human antibodies.

According to another aspect of the invention, a pharmaceutical composition containing a pharmaceutically effective amount of an isolated SOC/CRAC nucleic acid, an isolated SOC/CRAC polypeptide, or an isolated SOC/CRAC binding polypeptide in a pharmaceutically acceptable carrier also is provided. The pharmaceutical compositions are useful in accordance with therapeutic methods disclosed herein.

According to yet another aspect of the invention, a method for isolating a SOC/CRAC molecule is provided. The method involves:

a) contacting a SOC/CRAC nucleic acid or a SOC/CRAC binding polypeptide with a sample that is believed to contain one or more SOC/CRAC molecules, under conditions to form a complex of the SOC/CRAC nucleic acid or the SOC/CRAC binding polypeptide and the SOC/CRAC molecule;

b) detecting the presence of the complex;

c) isolating the SOC/CRAC molecule from the complex; and

d) determining whether the isolated SOC/CRAC molecule has SOC/CRAC calcium channel activity. As used herein "SOC/CRAC calcium channel activity" refers to the transport of Ca²⁺ into and out of intracellular stores that is mediated by a SOC/CRAC

polypeptide. In general, the SOC/CRAC calcium channel activity is initiated by a reduction or depletion of intracellular calcium stores.

In certain embodiments, the SOC/CRAC nucleic acid is a SOC-2/CRAC-1 nucleic acid (e.g., a nucleic acid having SEQ. ID NO. 27, or complements thereof); in certain other
5 embodiments, the SOC/CRAC nucleic acid is a SOC-3/CRAC-2 nucleic acid (e.g., a nucleic acid having SEQ. ID NO. 29, or complements thereof); in further embodiments, the SOC/CRAC nucleic acid is a SOC-4/CRAC-3 nucleic acid (e.g., a nucleic acid having SEQ. ID NO. 31, or complements thereof). In yet other embodiments, the SOC/CRAC polypeptide is a SOC-2/CRAC-1 binding polypeptide (e.g., an antibody that selectively binds to a SOC-
10 2/CRAC-1 polypeptide). In yet further embodiments, the SOC/CRAC polypeptide is a SOC-3/CRAC-2 binding polypeptide (e.g., an antibody that selectively binds to a SOC-3/CRAC-2 polypeptide). In some embodiments, the SOC/CRAC polypeptide is a SOC-4/CRAC-3 binding polypeptide (e.g., an antibody that selectively binds to a SOC-4/CRAC-3 polypeptide). In the preferred embodiments, the isolated binding polypeptides include
15 antibodies and fragments of antibodies (e.g., Fab, F(ab)₂, Fd and antibody fragments which include a CDR3 region which binds selectively to a SOC-2/CRAC-1, to a SOC-3/CRAC-2, and/or to a SOC-4/CRAC-3 polypeptide). Preferably the isolated binding polypeptides or other binding agents selectively bind to a single SOC/CRAC molecule, i.e., are capable of distinguishing between different members of the SOC/CRAC family. Accordingly, one or
20 more SOC/CRAC binding agents can be contained in a single composition (e.g., a pharmaceutical composition) to identify multiple SOC/CRAC molecules *in vivo* or *in vitro*.

According to yet another aspect of the invention, a method for identifying agents useful in the modulation of SOC/CRAC calcium channel activity is provided. The method involves:

- 25 a) contacting a SOC/CRAC polypeptide with a candidate agent suspected of modulating SOC/CRAC calcium channel activity, under conditions sufficient to allow the candidate agent to interact selectively with (e.g. bind to) the SOC/CRAC polypeptide;
- b) detecting a Ca²⁺ concentration of step (b) associated with the SOC/CRAC calcium channel activity of the SOC/CRAC polypeptide in the presence of the candidate agent; and
- 30 c) comparing the Ca²⁺ concentration of step (b) with a control Ca²⁺ concentration of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the candidate agent modulates (increases or decreases) SOC/CRAC calcium channel activity.

According to another aspect of the invention, a method for identifying agents useful in the modulation of a SOC/CRAC polypeptide kinase activity is provided. The method involves:

- a) contacting a SOC/CRAC polypeptide with kinase activity with a candidate agent suspected of modulating SOC/CRAC kinase activity, under conditions sufficient to allow the candidate agent to interact with the SOC/CRAC polypeptide and modulate its kinase activity;
- b) detecting a kinase activity associated with the SOC/CRAC polypeptide in the presence of the candidate agent; and
- c) comparing the kinase activity of step (b) with a control kinase activity of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the candidate agent modulates (increases or decreases) SOC/CRAC kinase activity. In some embodiments the SOC/CRAC polypeptide comprises amino acids 999-1180 of the SOC-2/CRAC-1 polypeptide (SEQ ID NO:24), or a fragment thereof that retains the kinase activity.

According to yet another aspect of the invention, a method for determining the level of expression of a SOC/CRAC polypeptide in a subject is provided. The method involves:

- a) measuring the expression of a SOC/CRAC polypeptide in a test sample, and
- b) comparing the measured expression of the SOC/CRAC polypeptide in the test sample to the expression of a SOC/CRAC polypeptide in a control containing a known level of expression to determine the level of SOC/CRAC expression in the subject. Expression is defined as SOC/CRAC mRNA expression or SOC/CRAC polypeptide expression. Various methods can be used to measure expression. The preferred embodiments of the invention utilize PCR and Northern blotting for measuring mRNA expression, and monoclonal or polyclonal SOC/CRAC antisera as reagents for measuring SOC/CRAC polypeptide expression. In preferred embodiments, the SOC/CRAC molecule (nucleic acid and/or polypeptide) is SOC-2/CRAC-1. In other preferred embodiments, the SOC/CRAC molecule is SOC-3/CRAC-2. In yet further preferred embodiments, the SOC/CRAC molecule is SOC-4/CRAC-3. In certain embodiments, the test samples include biopsy samples and biological fluids such as blood. The method is useful, e.g., for assessing the presence or absence or stage of a proliferative disorder in a subject.

The invention also contemplates kits comprising a package including assays for SOC/CRAC epitopes, SOC/CRAC nucleic acids, and instructions, and optionally related materials such as controls, for example, a number, color chart, or an epitope of the expression product of the foregoing isolated nucleic acid molecules of the invention for comparing, for

example, the level of SOC/CRAC polypeptides or SOC/CRAC nucleic acid forms (wild-type or mutant) in a test sample to the level in a control sample having a known amount of a SOC/CRAC nucleic acid or SOC/CRAC polypeptide. This comparison can be used to assess in a subject a risk of developing a cancer or the progression of a cancer. The kits may also include assays for other known genes, and expression products thereof, associated with, for example, proliferative disorders (e.g., BRCA, p53, etc.). In a preferred embodiment, the kit comprises a package containing: (a) a binding agent that selectively binds to an isolated nucleic acid of the invention or an expression product thereof to obtain a measured test value, (b) a control containing a known amount of a SOC/CRAC nucleic acid or a SOC/CRAC polypeptide to obtain a measured control value, and (c) instructions for comparing the measured test value to the measured control value to determine the amount of SOC/CRAC nucleic acid or expression product thereof in a sample.

The invention provides isolated nucleic acid molecules, unique fragments thereof, expression vectors containing the foregoing, and host cells containing the foregoing. The invention also provides isolated binding polypeptides and binding agents which bind such polypeptides, including antibodies, and pharmaceutical compositions containing any of the compositions of the invention. The foregoing can be used, *inter alia*, in the diagnosis or treatment of conditions characterized by the aberrant expression levels and/or the presence of mutant forms of a SOC/CRAC nucleic acid or polypeptide. The invention also provides methods for identifying agents that alter the function of the SOC/CRAC polypeptide.

These and other aspects of the invention, as well as various advantages and utilities, will be more apparent with reference to the detailed description of the preferred embodiments.

Brief Description of the Sequences

SEQ ID NO:1 is a partial nucleotide sequence of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:2 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:1).

SEQ ID NO:3 is a partial nucleotide sequence of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:4 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:3).

SEQ ID NO:5 is a partial nucleotide sequence of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:6 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:5).

SEQ ID NO:7 is a partial nucleotide sequence of the mouse homologue (mSOC-2/CRAC-1) of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:8 is the predicted amino acid sequence of the translation product of the mSOC-2/CRAC-1 cDNA (SEQ ID NO:7).

5 SEQ ID NO:9 is the nucleotide sequence of the mouse MLSN-1 (SOC-1) cDNA.

SEQ ID NO:10 is the predicted amino acid sequence of the translation product of the mouse MLSN-1 (SOC-1) cDNA (SEQ ID NO:9).

SEQ ID NO:11 is the nucleotide sequence of a human calcium channel cDNA with GenBank Acc. no.: AB001535.

10 SEQ ID NO:12 is the predicted amino acid sequence of the translation product of the human calcium channel cDNA with GenBank Acc. no.: AB001535 (SEQ ID NO:11).

SEQ ID NO:13 is the amino acid sequence of a *C. Elegans* polypeptide at the c05c12.3 locus.

15 SEQ ID NO:14 is the amino acid sequence of a *C. Elegans* polypeptide at the F54D1 locus.

SEQ ID NO:15 is the amino acid sequence of a *C. Elegans* polypeptide at the t01H8 locus.

SEQ ID NO:16 is the nucleotide sequence of a mouse kidney cDNA with GenBank Acc. no.: AI226731.

20 SEQ ID NO:17 is the predicted amino acid sequence of the translation product of the mouse kidney cDNA with GenBank Acc. no.: AI226731 (SEQ ID NO:16).

SEQ ID NO:18 is the nucleotide sequence of a human brain cDNA with GenBank Acc. no.: H18835.

25 SEQ ID NO:19 is the predicted amino acid sequence of the translation product of the human brain cDNA with GenBank Acc. no.: H18835 (SEQ ID NO:18).

SEQ ID NO:20 is the nucleotide sequence of the human EST with GenBank Acc. no.: AA419592.

SEQ ID NO:21 is the nucleotide sequence of the human EST with GenBank Acc. no.: AA419407.

30 SEQ ID NO:22 is the nucleotide sequence of the mouse EST with GenBank Acc. no.: AI098310.

-9-

SEQ ID NO:23 is a partial nucleotide sequence of the human SOC-2/CRAC-1 cDNA that contains the SOC-2/CRAC-1 sequences of SEQ ID NO:1, SEQ ID NO:3, and SEQ ID NO:5.

SEQ ID NO:24 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:23).

SEQ ID NO:25 is a partial nucleotide sequence of the human SOC-3/CRAC-2 cDNA.

SEQ ID NO:26 is the predicted amino acid sequence of the translation product of human SOC-3/CRAC-2 cDNA (SEQ ID NO:25).

SEQ ID NO:27 is the full nucleotide sequence of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:28 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:27).

SEQ ID NO:29 is the full nucleotide sequence of the human SOC-3/CRAC-2 cDNA.

SEQ ID NO:30 is the predicted amino acid sequence of the translation product of human SOC-3/CRAC-2 cDNA (SEQ ID NO:29).

SEQ ID NO:31 is the full nucleotide sequence of the human SOC-4/CRAC-3 cDNA.

SEQ ID NO:32 is the predicted amino acid sequence of the translation product of human SOC-4/CRAC-3 cDNA (SEQ ID NO:31).

Brief Description of the Drawings

Figure 1 is a schematic depicting the intron/exon organization of the chicken SOC-2/CRAC-1 genomic sequence, as well as the putative transmembrane (TM) domains, and the targeting constructs utilized in the knockout experiments.

Detailed Description of the Invention

One aspect of the invention involves the partial cloning of cDNAs encoding members of a novel family of calcium channel polypeptides, referred to herein as "SOC/CRAC" (designated "SOC" or "CRAC" or "ICRAC", for Sore Operated Channels or Calcium Release Activated Channels, or CECH). Although not intending to be bound to any particular mechanism or theory, we believe that a SOC/CRAC family member is a transmembrane calcium channel that modulates Ca^{2+} flux "into" and "out of" a cell; in certain instances it may be activated upon depletion of Ca^{2+} from intracellular calcium stores, allowing Ca^{2+} influx into the cell.

The first three isolated SOC/CRAC members disclosed herein, define a new family of calcium channels which is distinct from previously described calcium channels, such as voltage gated calcium channels, ryanodine receptor/inositol-1,4,5-triphosphate receptor

-10-

channels, and Transient Receptor Potential (TRP) channels. The SOC/CRAC family of calcium channels exhibits high selectivity (with a P_{Ca}/P_{Na} ratio near 1000), a unitary conductance below the detection level of the patch clamp method (the conductance estimated at approximately 0.2 picosiemens), and are subject to inhibition by high intracellular calcium levels. Although not intending to be bound to any particular mechanism or theory, we believe that SOC/CRAC calcium channels are responsible for the majority of, for example, calcium entry which occurs when intracellular calcium stores are depleted, and that SOC/CRAC currents are important for initiating various types of calcium-dependent processes. Thus, we believe that SOC/CRAC calcium channels play an important role in cellular calcium homeostasis by, e.g., modulating the supply of calcium to refill intracellular stores when depleted.

The isolated full-length sequence of a representative, first member of the SOC/CRAC family, human SOC/CRAC nucleic acid (cDNA), SOC-2/CRAC-1, is represented as the nucleic acid of SEQ ID NO:27. This nucleic acid sequence codes for the SOC-2/CRAC-1 polypeptide with the predicted amino acid sequence disclosed herein as SEQ ID NO:28. A homologous mouse cDNA sequence (>90% identity to the human at the nucleotide level) is represented as the nucleic acid of SEQ ID NO:7, and codes for a unique fragment of a mouse SOC-2/CRAC-1 polypeptide having the predicted, partial amino acid sequence represented as SEQ ID NO:8. Analysis of the SOC-2/CRAC-1 partial sequence by comparison to nucleic acid and protein databases show that SOC-2/CRAC-1 shares a limited homology to mouse MLSN-1 (SOC-1, SEQ ID NOs: 9 and 10). Limited homology is also shared between SOC-2/CRAC-1 and three *C. Elegans* polypeptides (SEQ ID NOs: 13, 14, and 15). We further believe that SOC-2/CRAC-1 plays a role in the regulation of cellular Ca^{2+} fluxing and, in particular, lymphocyte Ca^{2+} fluxing.

A second member of the human SOC/CRAC family of calcium channels, SOC-3/CRAC-2, is represented as the nucleic acid of SEQ ID NO:29, and codes for the human SOC-3/CRAC-2 polypeptide having the predicted amino acid sequence represented as SEQ ID NO:30 (this molecule may also be referred to as CECH2). SOC-3/CRAC-2 is predominantly expressed in human hematopoietic cells (including peripheral blood lymphocytes, liver, bone marrow, spleen, thymus, lymph nodes, heart, and kidney. Expression can also be detected (at lesser levels) in brain, skeletal muscle colon, small intestine, placenta, lung, and cells (cell lines) such as HL-60, HeLa, K562, MOLT-4, SW-480, A459, and G361.

A third member of the human SOC/CRAC family of calcium channels, SOC-4/CRAC-3, is represented as the nucleic acid of SEQ ID NO:31, and codes for the human SOC-4/CRAC-3 polypeptide having the predicted amino acid sequence represented as SEQ ID NO:32 (this molecule may also be referred to as CECH6). It specifically expressed in the prostate gland/cells.

As used herein, a SOC/CRAC calcium channel nucleic acid (also referred to herein as a "SOC/CRAC nucleic acid" refers to a nucleic acid molecule which: (1) hybridizes under stringent conditions to one or more of the nucleic acids having the sequences of SEQ. ID NOS. 7, 27, 29, and/or 31 (sequences of the mouse and human SOC-2/CRAC-1, human SOC-3/CRAC-2, and human SOC-4/CRAC-3 nucleic acids), and (2) codes for a SOC-2/CRAC-1, a SOC-3/CRAC-2 or a SOC-4/CRAC-3 calcium channel polypeptide, respectively, or unique fragments of said SOC-2/CRAC-1, SOC-3/CRAC-2, or SOC-4/CRAC-3 polypeptide.

As used herein, a SOC/CRAC calcium channel polypeptide (also referred to herein as a "SOC/CRAC polypeptide") refers to a polypeptide that is coded for by a SOC-2/CRAC-1, a SOC-3/CRAC-2, and/or a SOC-4/CRAC-3 nucleic acid. Preferably, the above-identified SOC/CRAC polypeptides mediate transport of calcium into and out of a cell.

SOC/CRAC polypeptides also are useful as immunogenic molecules for the generation of binding polypeptides (e.g., antibodies) which bind selectively to SOC/CRAC (e.g., SOC-2/CRAC-1, SOC-3/CRAC-2, and/or SOC-4/CRAC-3) polypeptides. Such antibodies can be used in diagnostic assays to identify and/or quantify the presence of a SOC/CRAC polypeptide in a sample, such as a biological fluid or biopsy sample. SOC/CRAC polypeptides further embrace functionally equivalent fragments, variants, and analogs of the preferred SOC/CRAC polypeptides, provided that the fragments, variants, and analogs also are useful in mediating calcium transport into and out of intracellular calcium stores.

As used herein, "SOC/CRAC calcium channel activity" refers to Ca^{2+} transport ("Ca²⁺ fluxing") across the plasma membrane that is mediated by a SOC/CRAC calcium channel polypeptide. The SOC/CRAC calcium channel polypeptide typically has one or more of the following properties: high selectivity, a unitary conductance below the detection level of the patch clamp method, and are subject to inhibition by high intracellular calcium levels. Such activity can be easily detected using standard methodology well known in the art. See, e.g., the Examples and Neher, E., "Ion channels for communication between and within cells",

Science, 1992; 256:498-502; and Hoth, M., and Penner, R., "Depletion of intracellular calcium stores activates a calcium current in mast cells", Nature, 1992; 355 (6358):353-6.

According to one aspect of the invention, isolated nucleic acid molecules which code for one or more member(s) of the SOC/CRAC family of calcium channel polypeptides are provided. The isolated nucleic acid molecules are selected from the following groups:

(a) nucleic acid molecules which hybridize under stringent conditions to one or more nucleic acid molecules selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, and which code for a SOC/CRAC polypeptide;

(b) deletions, additions and substitutions of (a) which code for a respective SOC/CRAC polypeptide;

(c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) in codon sequence due to the degeneracy of the genetic code, and

(d) complements of (a), (b) or (c).

In certain embodiments, the isolated nucleic acid molecule comprises one or more of nucleotides 1-1212 of SEQ ID NO:1; nucleotides 1-739 of SEQ ID NO:3; nucleotides 1-1579 of SEQ ID NO:5; nucleotides 1-5117 of SEQ ID NO:23; the mouse homolog for SOC-2/CRAC-1 corresponding to SEQ ID NO:7; nucleotides 1-2180 of SEQ ID NO:25; nucleotides 382-5976 of SEQ ID NO:27; nucleotides 73-3714 of SEQ ID NO:29; and nucleotides 23-3434 of SEQ ID NO:31. In yet other embodiments, the isolated nucleic acid molecule comprises a molecule which encodes a polypeptide having one or more sequences selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32.

According to yet another aspect of the invention, an isolated nucleic acid molecule is provided which is selected from the group consisting of:

(a) a unique fragment of a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, (of sufficient length to represent a sequence unique within the human genome); and (b) complements of (a), provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to a sequence in the prior art as represented by the sequence group consisting of: (1) sequences having the SEQ ID NOs or GenBank accession numbers of Table I, (2) complements of (1), and (3) fragments of (1) and (2).

In some embodiments, the sequence of contiguous nucleotides is selected from the group consisting of (1) at least two contiguous nucleotides nonidentical to the sequence group, (2) at least three contiguous nucleotides nonidentical to the sequence group, (3) at least four contiguous nucleotides nonidentical to the sequence group, (4) at least five contiguous
5 nucleotides nonidentical to the sequence group, (5) at least six contiguous nucleotides nonidentical to the sequence group, (6) at least seven contiguous nucleotides nonidentical to the sequence group.

In other embodiments, the unique fragment has a size selected from the group consisting of at least: 8 nucleotides, 10 nucleotides, 12 nucleotides, 14 nucleotides, 16
10 nucleotides, 18 nucleotides, 20, nucleotides, 22 nucleotides, 24 nucleotides, 26 nucleotides, 28 nucleotides, 30 nucleotides, 40 nucleotides, 50 nucleotides, 75 nucleotides, 100 nucleotides, 200 nucleotides, 1000 nucleotides and every integer length therebetween.

According to another aspect of the invention, expression vectors and host cells containing (e.g., transformed or transfected with) expression vectors comprising the nucleic
15 acid molecules disclosed herein operably linked to a promoter are provided. In certain preferred embodiments, the host cells are eukaryotic cells.

The isolated nucleic acid molecules disclosed herein have various utilities, including their use as probes and primers to identify additional members of the SOC/CRAC family of calcium channels, as diagnostic reagents for identifying the presence of SOC/CRAC
20 polypeptides in biological or other samples, and as agents for generating SOC/CRAC binding polypeptides (e.g., antibodies) that can be used as reagents in diagnostic and therapeutic assays to identify the presence, absence, and/or amounts of a SOC/CRAC nucleic acid or polypeptide in a biological or other sample.

As used herein with respect to nucleic acids, the term "isolated" means: (i) amplified
25 *in vitro* by, for example, polymerase chain reaction (PCR); (ii) recombinantly produced by cloning; (iii) purified, as by cleavage and gel separation; or (iv) synthesized by, for example, chemical synthesis. An isolated nucleic acid is one which is readily manipulatable by recombinant DNA techniques well known in the art. Thus, a nucleotide sequence contained in a vector in which 5' and 3' restriction sites are known or for which polymerase chain
30 reaction (PCR) primer sequences have been disclosed is considered isolated but a nucleic acid sequence existing in its native state in its natural host is not. An isolated nucleic acid may be substantially purified, but need not be. For example, a nucleic acid that is isolated within a cloning or expression vector is not pure in that it may comprise only a tiny percentage of the

material in the cell in which it resides. Such a nucleic acid is isolated, however, as the term is used herein because it is readily manipulatable by standard techniques known to those of ordinary skill in the art.

As used herein with respect to polypeptides (discussed below), the term "isolated" means separated from its native environment in sufficiently pure form so that it can be manipulated or used for any one of the purposes of the invention. Thus, isolated means sufficiently pure to be used (i) to raise and/or isolate antibodies, (ii) as a reagent in an assay, or (iii) for sequencing, etc.

Homologs and alleles of the SOC/CRAC nucleic acids of the invention can be identified by conventional techniques. Thus, an aspect of the invention is those nucleic acid sequences which code for SOC/CRAC polypeptides and which hybridize to a nucleic acid molecule selected from a group consisting of the nucleic acid of SEQ ID NO:1, the nucleic acid of SEQ ID NO:3, the nucleic acid of SEQ ID NO:5, the nucleic acid of SEQ ID NO:7, the nucleic acid of SEQ ID NO:23, the nucleic acid of SEQ ID NO:25, the nucleic acid of SEQ ID NO:27, the nucleic acid of SEQ ID NO:29, and the nucleic acid of SEQ ID NO:31, under stringent conditions. The term "stringent conditions" as used herein refers to parameters with which the art is familiar. Nucleic acid hybridization parameters may be found in references which compile such methods, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. More specifically, stringent conditions, as used herein, refers, for example, to hybridization at 65°C in hybridization buffer (3.5 x SSC, 0.02% Ficoll, 0.02% polyvinyl pyrrolidone, 0.02% Bovine Serum Albumin, 2.5mM NaH₂PO₄(pH7), 0.5% SDS, 2mM EDTA). SSC is 0.15M sodium chloride/0.15M sodium citrate, pH7; SDS is sodium dodecyl sulphate; and EDTA is ethylenediaminetetracetic acid. After hybridization, the membrane upon which the DNA is transferred is washed at 2 x SSC at room temperature and then at 0.1 x SSC/0.1 x SDS at temperatures up to 68°C.

There are other conditions, reagents, and so forth which can be used, and would result in a similar degree of stringency. The skilled artisan will be familiar with such conditions, and thus they are not given here. It will be understood, however, that the skilled artisan will be able to manipulate the conditions in a manner to permit the clear identification of homologs and alleles of the SOC/CRAC nucleic acids of the invention. The skilled artisan also is familiar with the methodology for screening cells and libraries for expression of such

molecules which then are routinely isolated, followed by isolation of the pertinent nucleic acid molecule and sequencing.

In general homologs and alleles typically will share at least 40% nucleotide identity and/or at least 50% amino acid identity to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and/or SEQ ID NO:31, and SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and/or SEQ ID NO:32, respectively. In some instances sequences will share at least 50% nucleotide identity and/or at least 65% amino acid identity and in still other instances sequences will share at least 60% nucleotide identity and/or at least 75% amino acid identity. The homology can be calculated using various, publicly available software tools developed by NCBI (Bethesda, Maryland) that can be obtained through the internet (<ftp://ncbi.nlm.nih.gov/pub/>). Exemplary tools include the BLAST system available at <http://www.ncbi.nlm.nih.gov>. Pairwise and ClustalW alignments (BLOSUM30 matrix setting) as well as Kyte-Doolittle hydropathic analysis can be obtained using the MacVetor sequence analysis software (Oxford Molecular Group). Watson-Crick complements of the foregoing nucleic acids also are embraced by the invention.

In screening for SOC/CRAC related genes, such as homologs and alleles of SOC-2/CRAC-1 and/or SOC-3/CRAC-2, a Southern blot may be performed using the foregoing conditions, together with a radioactive probe. After washing the membrane to which the DNA is finally transferred, the membrane can be placed against X-ray film or a phosphorimager plate to detect the radioactive signal.

Given that the expression of the SOC/CRAC gene is prominent in certain human tissues (e.g., SOC-2/CRAC-1: lymphoid tissue/heart, SOC-3/CRAC-2: kidney/colon, SOC-4/CRAC-3: prostate), and given the teachings herein of partial human SOC/CRAC cDNA clones, full-length and other mammalian sequences corresponding to the human SOC/CRAC partial nucleic acid sequences can be isolated from, for example, a cDNA library prepared from one or more of the tissues in which SOC-2/CRAC-1 expression is prominent, SOC-3/CRAC-2 is prominent, and/or SOC-4/CRAC-3 expression is prominent, using standard colony hybridization techniques.

The invention also includes degenerate nucleic acids which include alternative codons to those present in the native materials. For example, serine residues are encoded by the codons TCA, AGT, TCC, TCG, TCT and AGC. Each of the six codons is equivalent for the purposes of encoding a serine residue. Thus, it will be apparent to one of ordinary skill in the

art that any of the serine-encoding nucleotide triplets may be employed to direct the protein synthesis apparatus, *in vitro* or *in vivo*, to incorporate a serine residue into an elongating SOC/CRAC polypeptide. Similarly, nucleotide sequence triplets which encode other amino acid residues include, but are not limited to: CCA, CCC, CCG and CCT (proline codons); CGA, CGC, CGG, CGT, AGA and AGG (arginine codons); ACA, ACC, ACG and ACT (threonine codons); AAC and AAT (asparagine codons); and ATA, ATC and ATT (isoleucine codons). Other amino acid residues may be encoded similarly by multiple nucleotide sequences. Thus, the invention embraces degenerate nucleic acids that differ from the biologically isolated nucleic acids in codon sequence due to the degeneracy of the genetic code.

The invention also provides isolated unique fragments of an isolated nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31. A unique fragment is one that is a 'signature' for the larger nucleic acid. For example, the unique fragment is long enough to assure that its precise sequence is not found in molecules within the human genome outside of the SOC/CRAC nucleic acids defined above (and human alleles). Those of ordinary skill in the art may apply no more than routine procedures to determine if a fragment is unique within the human genome.

Unique fragments, however, exclude fragments completely composed of the nucleotide sequences of any of GenBank accession numbers and SEQ ID NOs listed in Table I (SEQ ID NO:9, AB001535, AI226731, H18835, AA419592, AA261842, AA419407, AI098310, AA592910, D86107, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, AC005538, AA654650, AA370110, AA313170, AA493512, AI670079, AI671853, AC005538, AA654650, AA370110, AA313170, AA493512, AI670079, AI671853), or other previously published sequences as of the filing date of this application.

A fragment which is completely composed of the sequence described in the foregoing GenBank deposits and SEQ ID NO:9, is one which does not include any of the nucleotides unique to the sequences of the invention. Thus, a unique fragment must contain a nucleotide sequence other than the exact sequence of those in GenBank or fragments thereof. The difference may be an addition, deletion or substitution with respect to the GenBank sequence or it may be a sequence wholly separate from the GenBank sequence.

Unique fragments can be used as probes in Southern and Northern blot assays to identify such nucleic acids, or can be used in amplification assays such as those employing PCR. As known to those skilled in the art, large probes such as 200, 250, 300 or more nucleotides are preferred for certain uses such as Southern and Northern blots, while smaller fragments will be preferred for uses such as PCR. Unique fragments also can be used to produce fusion proteins for generating antibodies or determining binding of the polypeptide fragments, as demonstrated in the Examples, or for generating immunoassay components. Likewise, unique fragments can be employed to produce nonfused fragments of the SOC/CRAC polypeptides, useful, for example, in the preparation of antibodies, immunoassays or therapeutic applications. Unique fragments further can be used as antisense molecules to inhibit the expression of SOC/CRAC nucleic acids and polypeptides, respectively.

As will be recognized by those skilled in the art, the size of the unique fragment will depend upon its conservancy in the genetic code. Thus, some regions of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, and complements thereof, will require longer segments to be unique while others will require only short segments, typically between 12 and 32 nucleotides long (e.g. 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 and 32 bases) or more, up to the entire length of the disclosed sequence. As mentioned above, this disclosure intends to embrace each and every fragment of each sequence, beginning at the first nucleotide, the second nucleotide and so on, up to 8 nucleotides short of the end, and ending anywhere from nucleotide number 8, 9, 10 and so on for each sequence, up to the very last nucleotide, (provided the sequence is unique as described above). Virtually any segment of the region of SEQ ID NO:1 beginning at nucleotide 1 and ending at nucleotide 1212, or SEQ ID NO:3 beginning at nucleotide 1 and ending at nucleotide 739, or SEQ ID NO:5 beginning at nucleotide 1 and ending at nucleotide 1579, or SEQ ID NO:7 beginning at nucleotide 1 and ending at nucleotide 3532, or SEQ ID NO:23 beginning at nucleotide 1 and ending at nucleotide 5117, SEQ ID NO:25 beginning at nucleotide 1 and ending at nucleotide 2180, SEQ ID NO:27 beginning at nucleotide 1 and ending at nucleotide 7419, or SEQ ID NO:29 beginning at nucleotide 1 and ending at nucleotide 4061, or SEQ ID NO:31 beginning at nucleotide 1 and ending at nucleotide 4646, or complements thereof, that is 20 or more nucleotides in length will be unique. Those skilled in the art are well versed in methods for selecting such sequences, typically on the basis of the ability of the unique

fragment to selectively distinguish the sequence of interest from other sequences in the human genome of the fragment to those on known databases typically is all that is necessary, although *in vitro* confirmatory hybridization and sequencing analysis may be performed.

As mentioned above, the invention embraces antisense oligonucleotides that
5 selectively bind to a nucleic acid molecule encoding a SOC/CRAC polypeptide, to decrease SOC/CRAC calcium channel activity. When using antisense preparations of the invention, slow intravenous administration is preferred.

As used herein, the term "antisense oligonucleotide" or "antisense" describes an oligonucleotide that is an oligoribonucleotide, oligodeoxyribonucleotide, modified
10 oligoribonucleotide, or modified oligodeoxyribonucleotide which hybridizes under physiological conditions to DNA comprising a particular gene or to an mRNA transcript of that gene and, thereby, inhibits the transcription of that gene and/or the translation of that mRNA. The antisense molecules are designed so as to interfere with transcription or translation of a target gene upon hybridization with the target gene or transcript. Those
15 skilled in the art will recognize that the exact length of the antisense oligonucleotide and its degree of complementarity with its target will depend upon the specific target selected, including the sequence of the target and the particular bases which comprise that sequence. It is preferred that the antisense oligonucleotide be constructed and arranged so as to bind selectively with the target under physiological conditions, i.e., to hybridize substantially more
20 to the target sequence than to any other sequence in the target cell under physiological conditions. Based upon SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, or upon allelic or homologous genomic and/or cDNA sequences, one of skill in the art can easily choose and synthesize any of a number of appropriate antisense molecules for use in accordance with the
25 present invention. In order to be sufficiently selective and potent for inhibition, such antisense oligonucleotides should comprise at least 10 and, more preferably, at least 15 consecutive bases which are complementary to the target, although in certain cases modified oligonucleotides as short as 7 bases in length have been used successfully as antisense oligonucleotides (Wagner et al., *Nat. Med.* 1(11):1116-1118, 1995). Most preferably, the
30 antisense oligonucleotides comprise a complementary sequence of 20-30 bases. Although oligonucleotides may be chosen which are antisense to any region of the gene or mRNA transcripts, in preferred embodiments the antisense oligonucleotides correspond to N-terminal or 5' upstream sites such as translation initiation, transcription initiation or promoter sites. In

addition, 3'-untranslated regions may be targeted by antisense oligonucleotides. Targeting to mRNA splicing sites has also been used in the art but may be less preferred if alternative mRNA splicing occurs. In addition, the antisense is targeted, preferably, to sites in which mRNA secondary structure is not expected (see, e.g., Sainio et al., *Cell Mol. Neurobiol.* 14(5):439-457, 1994) and at which proteins are not expected to bind. Finally, although, SEQ ID No:1 discloses a cDNA sequence, one of ordinary skill in the art may easily derive the genomic DNA corresponding to this sequence. Thus, the present invention also provides for antisense oligonucleotides which are complementary to the genomic DNA corresponding to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31. Similarly, antisense to allelic or homologous SOC/CRAC cDNAs and genomic DNAs are enabled without undue experimentation.

In one set of embodiments, the antisense oligonucleotides of the invention may be composed of "natural" deoxyribonucleotides, ribonucleotides, or any combination thereof. That is, the 5' end of one native nucleotide and the 3' end of another native nucleotide may be covalently linked, as in natural systems, via a phosphodiester internucleoside linkage. These oligonucleotides may be prepared by art recognized methods which may be carried out manually or by an automated synthesizer. They also may be produced recombinantly by vectors.

In preferred embodiments, however, the antisense oligonucleotides of the invention also may include "modified" oligonucleotides. That is, the oligonucleotides may be modified in a number of ways which do not prevent them from hybridizing to their target but which enhance their stability or targeting or which otherwise enhance their therapeutic effectiveness.

The term "modified oligonucleotide" as used herein describes an oligonucleotide in which (1) at least two of its nucleotides are covalently linked via a synthetic internucleoside linkage (i.e., a linkage other than a phosphodiester linkage between the 5' end of one nucleotide and the 3' end of another nucleotide) and/or (2) a chemical group not normally associated with nucleic acids has been covalently attached to the oligonucleotide. Preferred synthetic internucleoside linkages are phosphorothioates, alkylphosphonates, phosphorodithioates, phosphate esters, alkylphosphonothioates, phosphoramidates, carbamates, carbonates, phosphate triesters, acetamidates, carboxymethyl esters and peptides.

The term "modified oligonucleotide" also encompasses oligonucleotides with a covalently modified base and/or sugar. For example, modified oligonucleotides include

oligonucleotides having backbone sugars which are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 3' position and other than a phosphate group at the 5' position. Thus modified oligonucleotides may include a 2'-O-alkylated ribose group. In addition, modified oligonucleotides may include sugars such as arabinose instead of ribose. The present invention, thus, contemplates pharmaceutical preparations containing modified antisense molecules that are complementary to and hybridizable with, under physiological conditions, nucleic acids encoding SOC/CRAC polypeptides, together with pharmaceutically acceptable carriers. Antisense oligonucleotides may be administered as part of a pharmaceutical composition. Such a pharmaceutical composition may include the antisense oligonucleotides in combination with any standard physiologically and/or pharmaceutically acceptable carriers which are known in the art. The compositions should be sterile and contain a therapeutically effective amount of the antisense oligonucleotides in a unit of weight or volume suitable for administration to a patient. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients. The term "physiologically acceptable" refers to a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism. The characteristics of the carrier will depend on the route of administration. Physiologically and pharmaceutically acceptable carriers include diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials which are well known in the art.

The invention also involves expression vectors coding for SOC/CRAC proteins and fragments and variants thereof and host cells containing those expression vectors. Virtually any cells, prokaryotic or eukaryotic, which can be transformed with heterologous DNA or RNA and which can be grown or maintained in culture, may be used in the practice of the invention. Examples include bacterial cells such as E.coli and eukaryotic cells such as mouse, hamster, pig, goat, primate, yeast, xenopous, etc. They may be of a wide variety of tissue types, including mast cells, fibroblasts, oocytes and lymphocytes, and they may be primary cells or cell lines. Specific examples include CHO cells and COS cells. Cell-free transcription systems also may be used in lieu of cells.

As used herein, a "vector" may be any of a number of nucleic acids into which a desired sequence may be inserted by restriction and ligation for transport between different genetic environments or for expression in a host cell. Vectors are typically composed of DNA although RNA vectors are also available. Vectors include, but are not limited to,

plasmids, phagemids and virus genomes. A cloning vector is one which is able to replicate in a host cell, and which is further characterized by one or more endonuclease restriction sites at which the vector may be cut in a determinable fashion and into which a desired DNA sequence may be ligated such that the new recombinant vector retains its ability to replicate in the host cell. In the case of plasmids, replication of the desired sequence may occur many times as the plasmid increases in copy number within the host bacterium or just a single time per host before the host reproduces by mitosis. In the case of phage, replication may occur actively during a lytic phase or passively during a lysogenic phase. An expression vector is one into which a desired DNA sequence may be inserted by restriction and ligation such that it is operably joined to regulatory sequences and may be expressed as an RNA transcript. Vectors may further contain one or more marker sequences suitable for use in the identification of cells which have or have not been transformed or transfected with the vector. Markers include, for example, genes encoding proteins which increase or decrease either resistance or sensitivity to antibiotics or other compounds, genes which encode enzymes whose activities are detectable by standard assays known in the art (e.g., β -galactosidase or alkaline phosphatase), and genes which visibly affect the phenotype of transformed or transfected cells, hosts, colonies or plaques (e.g., green fluorescent protein). Preferred vectors are those capable of autonomous replication and expression of the structural gene products present in the DNA segments to which they are operably joined.

As used herein, a coding sequence and regulatory sequences are said to be "operably" joined when they are covalently linked in such a way as to place the expression or transcription of the coding sequence under the influence or control of the regulatory sequences. If it is desired that the coding sequences be translated into a functional protein, two DNA sequences are said to be operably joined if induction of a promoter in the 5' regulatory sequences results in the transcription of the coding sequence and if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter region to direct the transcription of the coding sequences, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. Thus, a promoter region would be operably joined to a coding sequence if the promoter region were capable of effecting transcription of that DNA sequence such that the resulting transcript might be translated into the desired protein or polypeptide.

The precise nature of the regulatory sequences needed for gene expression may vary between species or cell types, but shall in general include, as necessary, 5' non-transcribed

and 5' non-translated sequences involved with the initiation of transcription and translation respectively, such as a TATA box, capping sequence, CAAT sequence, and the like. Especially, such 5' non-transcribed regulatory sequences will include a promoter region which includes a promoter sequence for transcriptional control of the operably joined gene.

5 Regulatory sequences may also include enhancer sequences or upstream activator sequences as desired. The vectors of the invention may optionally include 5' leader or signal sequences. The choice and design of an appropriate vector is within the ability and discretion of one of ordinary skill in the art.

According to yet another aspect of the invention, isolated SOC/CRAC polypeptides
10 are provided. Preferably, the isolated SOC/CRAC polypeptides are encoded by the isolated SOC/CRAC nucleic acid molecules disclosed herein. More preferably, the isolated SOC/CRAC polypeptides of the invention are encoded by the nucleic acid molecules having SEQ ID Nos. 1, 3, 5, 7, 23, 25, 27, 29, and 31. In yet other embodiments, the isolated SOC/CRAC polypeptides of the invention have an amino acid sequence selected from the
15 group consisting of SEQ ID Nos. 2, 4, 6, 8, 24, 26, 28, 30 and 32. Preferably, the isolated SOC/CRAC polypeptides are of sufficient length to represent a sequence unique within the human genome. Thus, the preferred embodiments include a sequence of contiguous amino acids which is not identical to a prior art sequence as represented by the sequence group consisting of the contiguous amino acids identified in Table II (SEQ ID NO:10, SEQ ID
20 NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19 and GenBank Acc. Nos. AB001535, AA592910, D86107, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, NP003298, CAB00861, NP002411, CAA92726, CAB05572).

In certain embodiments, the isolated SOC/CRAC polypeptides are immunogenic and
25 can be used to generate binding polypeptides (e.g., antibodies) for use in diagnostic and therapeutic applications. Such binding polypeptides also are useful for detecting the presence, absence, and/or amounts of a SOC/CRAC nucleic acid or polypeptide in a sample such as a biological fluid or biopsy sample. Preferably, the SOC/CRAC polypeptides that are useful for generating binding polypeptides are unique polypeptides and, therefore, binding of the
30 antibody to a SOC/CRAC polypeptide in a sample is selective for the SOC/CRAC polypeptide.

Expression vectors containing all the necessary elements for expression are commercially available and known to those skilled in the art. See, e.g., Sambrook et al.,

Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989. Cells are genetically engineered by the introduction into the cells of heterologous DNA (RNA) encoding a SOC/CRAC polypeptide or fragment or variant thereof. The heterologous DNA (RNA) is placed under operable control of transcriptional elements to permit the expression of the heterologous DNA in the host cell.

Preferred systems for mRNA expression in mammalian cells are those such as pRc/CMV (available from Invitrogen, Carlsbad, CA) that contain a selectable marker such as a gene that confers G418 resistance (which facilitates the selection of stably transfected cell lines) and the human cytomegalovirus (CMV) enhancer-promoter sequences. Additionally, suitable for expression in primate or canine cell lines is the pCEP4 vector (Invitrogen, Carlsbad, CA), which contains an Epstein Barr virus (EBV) origin of replication, facilitating the maintenance of plasmid as a multicopy extrachromosomal element. Another expression vector is the pEF-BOS plasmid containing the promoter of polypeptide Elongation Factor 1 α , which stimulates efficiently transcription *in vitro*. The plasmid is described by Mishizuma and Nagata (*Nuc. Acids Res.* 18:5322, 1990), and its use in transfection experiments is disclosed by, for example, Demoulin (*Mol. Cell. Biol.* 16:4710-4716, 1996). Still another preferred expression vector is an adenovirus, described by Stratford-Perricaudet, which is defective for E1 and E3 proteins (*J. Clin. Invest.* 90:626-630, 1992). The use of the adenovirus as an Adeno.P1A recombinant is disclosed by Warnier et al., in intradermal injection in mice for immunization against P1A (*Int. J. Cancer*, 67:303-310, 1996).

The invention also embraces so-called expression kits, which allow the artisan to prepare a desired expression vector or vectors. Such expression kits include at least separate portions of each of the previously discussed coding sequences. Other components may be added, as desired, as long as the previously mentioned sequences, which are required, are included.

It will also be recognized that the invention embraces the use of the above described, SOC/CRAC cDNA sequence containing expression vectors, to transfect host cells and cell lines, by these prokaryotic (e.g., *E. coli*), or eukaryotic (e.g., CHO cells, COS cells, yeast expression systems and recombinant baculovirus expression in insect cells). Especially useful are mammalian cells such as mouse, hamster, pig, goat, primate, etc. They may be of a wide variety of tissue types, and include primary cells and cell lines. Specific examples include dendritic cells, U293 cells, peripheral blood leukocytes, bone marrow stem cells and embryonic stem cells. The invention also permits the construction of SOC/CRAC gene

"knock-outs" in cells and in animals, providing materials for studying certain aspects of SOC/CRAC calcium channel activity.

The invention also provides isolated polypeptides (including whole proteins and partial proteins), encoded by the foregoing SOC/CRAC nucleic acids, and include the polypeptides of SEQ ID NO:2, 4, 6, 8, 24, 26, 28, 30, 32, and unique fragments thereof. Such polypeptides are useful, for example, to regulate calcium transport-mediated cell growth, differentiation and proliferation, to generate antibodies, as components of immunoassays, etc. Polypeptides can be isolated from biological samples including tissue or cell homogenates, and can also be expressed recombinantly in a variety of prokaryotic and eukaryotic expression systems by constructing an expression vector appropriate to the expression system, introducing the expression vector into the expression system, and isolating the recombinantly expressed protein. Short polypeptides, including antigenic peptides (such as are presented by MHC molecules on the surface of a cell for immune recognition) also can be synthesized chemically using well-established methods of peptide synthesis.

A unique fragment of a SOC/CRAC polypeptide, in general, has the features and characteristics of unique fragments as discussed above in connection with nucleic acids. As will be recognized by those skilled in the art, the size of the unique fragment will depend upon factors such as whether the fragment constitutes a portion of a conserved protein domain. Thus, some regions of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and/or SEQ ID NO:32, will require longer segments to be unique while others will require only short segments, typically between 5 and 12 amino acids (e.g. 5, 6, 7, 8, 9, 10, 11 and 12 amino acids long or more, including each integer up to the full length, >1,000 amino acids long). Virtually any segment of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and/or SEQ ID NO:32, excluding the ones that share identity with it (the polypeptides identified in Table II - SEQ ID NO:10, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, and GenBank Acc. Nos. AB001535, AA592910, D86107, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, NP003298, CAB00861, NP002411, CAA92726, CAB05572) that is 9 or more amino acids in length will be unique.

Unique fragments of a polypeptide preferably are those fragments which retain a distinct functional capability of the polypeptide. Functional capabilities which can be retained in a unique fragment of a polypeptide include Ca^{2+} fluxing, high selectivity, a unitary

conductance below the detection level of the patch clamp method, and/or and are subject to inhibition by high intracellular calcium levels.

One important aspect of a unique fragment is its ability to act as a signature for identifying the polypeptide. Optionally, another aspect of a unique fragment is its ability to provide an immune response in an animal. Those skilled in the art are well versed in methods for selecting unique amino acid sequences, typically on the basis of the ability of the unique fragment to selectively distinguish the sequence of interest from non-family members. A comparison of the sequence of the fragment to those on known databases typically is all that is necessary.

The invention embraces variants of the SOC/CRAC polypeptides described above. As used herein, a "variant" of a SOC/CRAC polypeptide is a polypeptide which contains one or more modifications to the primary amino acid sequence of a SOC/CRAC polypeptide. Modifications which create a SOC/CRAC polypeptide variant are typically made to the nucleic acid which encodes the SOC/CRAC polypeptide, and can include deletions, point mutations, truncations, amino acid substitutions and addition of amino acids or non-amino acid moieties to:

- 1) reduce or eliminate a calcium channel activity of a SOC/CRAC polypeptide;
- 2) enhance a property of a SOC/CRAC polypeptide, such as protein stability in an expression system or the stability of protein-protein binding;
- 3) provide a novel activity or property to a SOC/CRAC polypeptide, such as addition of an antigenic epitope or addition of a detectable moiety; or
- 4) to provide equivalent or better binding to a SOC/CRAC polypeptide receptor or other molecule.

Alternatively, modifications can be made directly to the polypeptide, such as by cleavage, addition of a linker molecule, addition of a detectable moiety, such as biotin, addition of a fatty acid, and the like. Modifications also embrace fusion proteins comprising all or part of the SOC/CRAC amino acid sequence. One of skill in the art will be familiar with methods for predicting the effect on protein conformation of a change in protein sequence, and can thus "design" a variant SOC/CRAC polypeptide according to known methods. One example of such a method is described by Dahiyat and Mayo in *Science* 278:82-87, 1997, whereby proteins can be designed *de novo*. The method can be applied to a known protein to vary only a portion of the polypeptide sequence. By applying the computational methods of Dahiyat and Mayo, specific variants of a SOC/CRAC calcium channel polypeptide can be proposed and tested to determine whether the variant retains a desired conformation.

Variants can include SOC/CRAC polypeptides which are modified specifically to alter a feature of the polypeptide unrelated to its physiological activity. For example, cysteine residues can be substituted or deleted to prevent unwanted disulfide linkages. Similarly, certain amino acids can be changed to enhance expression of a SOC/CRAC polypeptide by eliminating proteolysis by proteases in an expression system (e.g., dibasic amino acid residues in yeast expression systems in which KEX2 protease activity is present).

Mutations of a nucleic acid which encodes a SOC/CRAC polypeptide preferably preserve the amino acid reading frame of the coding sequence and, preferably, do not create regions in the nucleic acid which are likely to hybridize to form secondary structures, such as hairpins or loops, which can be deleterious to expression of the variant polypeptide.

Mutations can be made by selecting an amino acid substitution, or by random mutagenesis of a selected site in a nucleic acid which encodes the polypeptide. Variant polypeptides are then expressed and tested for one or more activities to determine which mutation provides a variant polypeptide with the desired properties. Further mutations can be made to variants (or to non-variant SOC/CRAC polypeptides) which are silent as to the amino acid sequence of the polypeptide, but which provide preferred codons for translation in a particular host. The preferred codons for translation of a nucleic acid in, e.g., *E. coli*, are well known to those of ordinary skill in the art. Still other mutations can be made to the noncoding sequences of a SOC/CRAC gene or cDNA clone to enhance expression of the polypeptide.

The skilled artisan will realize that conservative amino acid substitutions may be made in SOC/CRAC polypeptides to provide functionally equivalent variants of the foregoing polypeptides, i.e., the variants retain the functional capabilities of the SOC/CRAC polypeptides. As used herein, a "conservative amino acid substitution" refers to an amino acid substitution which does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Variants can be prepared according to methods for altering polypeptide sequence known to one of ordinary skill in the art such as are found in references which compile such methods, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. Exemplary functionally equivalent variants of the SOC/CRAC polypeptides include conservative amino acid substitutions of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and/or SEQ ID NO:32. Conservative substitutions of amino acids

include substitutions made amongst amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q, N; and (g) E, D.

Thus functionally equivalent variants of SOC/CRAC polypeptides, i.e., variants of SOC/CRAC polypeptides which retain the function of the natural SOC/CRAC polypeptides, are contemplated by the invention. Conservative amino-acid substitutions in the amino acid sequence of SOC/CRAC polypeptides to produce functionally equivalent variants of SOC/CRAC polypeptides typically are made by alteration of a nucleic acid encoding SOC/CRAC polypeptides (e.g., SEQ ID NOs:1, 3, 5, 7, 23, 25, 27, 29, 31). Such substitutions can be made by a variety of methods known to one of ordinary skill in the art. For example, amino acid substitutions may be made by PCR-directed mutation, site-directed mutagenesis according to the method of Kunkel (Kunkel, *Proc. Nat. Acad. Sci. U.S.A.* 82: 488-492, 1985), or by chemical synthesis of a gene encoding a SOC/CRAC polypeptide. The activity of functionally equivalent fragments of SOC/CRAC polypeptides can be tested by cloning the gene encoding the altered SOC/CRAC polypeptide into a bacterial or mammalian expression vector, introducing the vector into an appropriate host cell, expressing the altered SOC/CRAC polypeptide, and testing for a functional capability of the SOC/CRAC polypeptides as disclosed herein (e.g., SOC/CRAC calcium channel activity).

The invention as described herein has a number of uses, some of which are described elsewhere herein. First, the invention permits isolation of SOC/CRAC polypeptides, including the isolation of the complete SOC/CRAC polypeptide. A variety of methodologies well-known to the skilled practitioner can be utilized to obtain isolated SOC/CRAC molecules. The polypeptide may be purified from cells which naturally produce the polypeptide by chromatographic means or immunological recognition. Alternatively, an expression vector may be introduced into cells to cause production of the polypeptide. In another method, mRNA transcripts may be microinjected or otherwise introduced into cells to cause production of the encoded polypeptide. Translation of SOC/CRAC mRNA in cell-free extracts such as the reticulocyte lysate system also may be used to produce SOC/CRAC polypeptides. Those skilled in the art also can readily follow known methods for isolating SOC/CRAC polypeptides. These include, but are not limited to, immunochromatography, HPLC, size-exclusion chromatography, ion-exchange chromatography and immune-affinity chromatography.

The invention also provides, in certain embodiments, "dominant negative" polypeptides derived from SOC/CRAC polypeptides. A dominant negative polypeptide is an

inactive variant of a protein, which, by interacting with the cellular machinery, displaces an active protein from its interaction with the cellular machinery or competes with the active protein, thereby reducing the effect of the active protein. For example, a dominant negative receptor which binds a ligand but does not transmit a signal in response to binding of the ligand can reduce the biological effect of expression of the ligand. Likewise, a dominant negative inactive SOC/CRAC calcium channel which interacts normally with the cell membrane but which does not mediate calcium transport can reduce calcium transport in a cell. Similarly, a dominant negative transcription factor which binds to a promoter site in the control region of a gene but does not increase gene transcription can reduce the effect of a normal transcription factor by occupying promoter binding sites without increasing transcription.

The end result of the expression of a dominant negative polypeptide in a cell is a reduction in function of active proteins. One of ordinary skill in the art can assess the potential for a dominant negative variant of a protein, and using standard mutagenesis techniques to create one or more dominant negative variant polypeptides. See, e.g., U.S. Patent No. 5,580,723 and Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press. The skilled artisan then can test the population of mutagenized polypeptides for diminution in a selected and/or for retention of such an activity. Other similar methods for creating and testing dominant negative variants of a protein will be apparent to one of ordinary skill in the art.

According to another aspect, the invention provides a method for isolating a SOC/CRAC molecule having SOC/CRAC calcium channel activity. The method involves contacting a binding molecule that is a SOC/CRAC nucleic acid or a SOC/CRAC binding polypeptide with a sample containing one or more SOC/CRAC molecules under conditions that allow such binding (see earlier discussion) to form a complex, detecting the presence of the complex, isolating the SOC/CRAC molecule from the complex, and determining whether the isolated SOC/CRAC molecule has SOC/CRAC calcium channel activity. Thus, the invention is useful for identifying and isolating full length complementary (cDNA) or genomic nucleic acids encoding SOC/CRAC polypeptides having SOC/CRAC calcium channel activity. Identification and isolation of such nucleic acids and polypeptides may be accomplished by hybridizing/binding, under appropriate conditions well known in the art, libraries and/or restriction enzyme-digested human nucleic acids, with a labeled SOC/CRAC molecular probe. As used herein, a "label" includes molecules that are incorporated into, for

example, a SOC/CRAC molecule (nucleic acid or peptide), that can be directly or indirectly detected. A wide variety of detectable labels are well known in the art that can be used, and include labels that provide direct detection (e.g., radioactivity, luminescence, optical or electron density, etc), or indirect detection (e.g., epitope tag such as the FLAG epitope, enzyme tag such as horseshoe peroxidase, etc.). The label may be bound to a SOC/CRAC binding partner, or incorporated into the structure of the binding partner.

A variety of methods may be used to detect the label, depending on the nature of the label and other assay components. For example, the label may be detected while bound to the solid substrate or subsequent to separation from the solid substrate. Labels may be directly detected through optical or electron density, radioactive emissions, nonradioactive energy transfers, etc. or indirectly detected with antibody conjugates, streptavidin-biotin conjugates, etc. Methods for detecting the labels are well known in the art. Once a library clone or hybridizing fragment is identified in the hybridization/binding reaction, it can be further isolated by employing standard isolation/cloning techniques known to those of skill in the art. See, generally, Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*, 2nd Edition, Cold Spring Harbor Laboratory Press. In addition, nucleic acid amplification techniques well known in the art, may also be used to locate splice variants of calcium channel (or calcium channel subunits) with SOC/CRAC calcium channel activity. Size and sequence determinations of the amplification products can reveal splice variants.

The foregoing isolated nucleic acids and polypeptides may then be compared to the nucleic acids and polypeptides of the present invention in order to identify homogeneity or divergence of the sequences, and be further characterized functionally to determine whether they belong to a family of molecules with SOC/CRAC calcium channel activity (for methodology see under the Examples section).

The isolation of the SOC/CRAC cDNA and/or partial sequences thereof also makes it possible for the artisan to diagnose a disorder characterized by an aberrant expression of SOC/CRAC. These methods involve determining expression of the SOC/CRAC gene, and/or SOC/CRAC polypeptides derived therefrom. In the former situation, such determinations can be carried out via any standard nucleic acid determination assay, including the polymerase chain reaction, or assaying with labeled hybridization probes as exemplified below. In the latter situation, such determination can be carried out via any standard immunological assay using, for example, antibodies which bind to the SOC/CRAC protein.

The invention also embraces isolated peptide binding agents which, for example, can be antibodies or fragments of antibodies ("binding polypeptides"), having the ability to selectively bind to SOC/CRAC polypeptides. Antibodies include polyclonal and monoclonal antibodies, prepared according to conventional methodology. In certain embodiments, the invention excludes binding agents (e.g., antibodies) that bind to the polypeptides encoded by the nucleic acids of SEQ ID NOs: 10, 12, 13, 14, 15, 17, and 19.

Significantly, as is well-known in the art, only a small portion of an antibody molecule, the paratope, is involved in the binding of the antibody to its epitope (see, in general, Clark, W.R. (1986) The Experimental Foundations of Modern Immunology Wiley & Sons, Inc., New York; Roitt, I. (1991) Essential Immunology, 7th Ed., Blackwell Scientific Publications, Oxford). The pFc' and Fc regions, for example, are effectors of the complement cascade but are not involved in antigen binding. An antibody from which the pFc' region has been enzymatically cleaved, or which has been produced without the pFc' region, designated an F(ab')₂ fragment, retains both of the antigen binding sites of an intact antibody. Similarly, an antibody from which the Fc region has been enzymatically cleaved, or which has been produced without the Fc region, designated an Fab fragment, retains one of the antigen binding sites of an intact antibody molecule. Proceeding further, Fab fragments consist of a covalently bound antibody light chain and a portion of the antibody heavy chain denoted Fd. The Fd fragments are the major determinant of antibody specificity (a single Fd fragment may be associated with up to ten different light chains without altering antibody specificity) and Fd fragments retain epitope-binding ability in isolation.

Within the antigen-binding portion of an antibody, as is well-known in the art, there are complementarity determining regions (CDRs), which directly interact with the epitope of the antigen, and framework regions (FRs), which maintain the tertiary structure of the paratope (see, in general, Clark, 1986; Roitt, 1991). In both the heavy chain Fd fragment and the light chain of IgG immunoglobulins, there are four framework regions (FR1 through FR4) separated respectively by three complementarity determining regions (CDR1 through CDR3). The CDRs, and in particular the CDR3 regions, and more particularly the heavy chain CDR3, are largely responsible for antibody specificity.

It is now well-established in the art that the non-CDR regions of a mammalian antibody may be replaced with similar regions of conspecific or heterospecific antibodies while retaining the epitopic specificity of the original antibody. This is most clearly manifested in the development and use of "humanized" antibodies in which non-human CDRs

are covalently joined to human FR and/or Fc/pFc' regions to produce a functional antibody. Thus, for example, PCT International Publication Number WO 92/04381 teaches the production and use of humanized murine RSV antibodies in which at least a portion of the murine FR regions have been replaced by FR regions of human origin. Such antibodies,
5 including fragments of intact antibodies with antigen-binding ability, are often referred to as "chimeric" antibodies.

Thus, as will be apparent to one of ordinary skill in the art, the present invention also provides for F(ab')₂, Fab, Fv and Fd fragments; chimeric antibodies in which the Fc and/or FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by
10 homologous human or non-human sequences; chimeric F(ab')₂ fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric Fab fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; and chimeric Fd fragment antibodies in which
15 the FR and/or CDR1 and/or CDR2 regions have been replaced by homologous human or non-human sequences. The present invention also includes so-called single chain antibodies.

Thus, the invention involves binding polypeptides of numerous size and type that bind selectively to SOC/CRAC polypeptides, and complexes containing SOC/CRAC polypeptides. These binding polypeptides also may be derived also from sources other than antibody
20 technology. For example, such polypeptide binding agents can be provided by degenerate peptide libraries which can be readily prepared in solution, in immobilized form, as bacterial flagella peptide display libraries or as phage display libraries. Combinatorial libraries also can be synthesized of peptides containing one or more amino acids. Libraries further can be synthesized of peptides and non-peptide synthetic moieties.

Phage display can be particularly effective in identifying binding peptides useful according to the invention. Briefly, one prepares a phage library (using e.g. m13, fd, or lambda phage), displaying inserts from 4 to about 80 amino acid residues using conventional
25 procedures. The inserts may represent, for example, a completely degenerate or biased array. One then can select phage-bearing inserts which bind to the SOC/CRAC polypeptide or a complex containing a SOC/CRAC polypeptide. This process can be repeated through several
30 cycles of reselection of phage that bind to the SOC/CRAC polypeptide or complex. Repeated rounds lead to enrichment of phage bearing particular sequences. DNA sequence analysis can be conducted to identify the sequences of the expressed polypeptides. The minimal linear

portion of the sequence that binds to the SOC/CRAC polypeptide or complex can be determined. One can repeat the procedure using a biased library containing inserts containing part or all of the minimal linear portion plus one or more additional degenerate residues upstream or downstream thereof. Yeast two-hybrid screening methods also may be used to
5 identify polypeptides that bind to the SOC/CRAC polypeptides. Thus, the SOC/CRAC polypeptides of the invention, or a fragment thereof, or complexes of SOC/CRAC can be used to screen peptide libraries, including phage display libraries, to identify and select peptide binding polypeptides that selectively bind to the SOC/CRAC polypeptides of the invention. Such molecules can be used, as described, for screening assays, for purification protocols, for
10 interfering directly with the functioning of SOC/CRAC and for other purposes that will be apparent to those of ordinary skill in the art.

A SOC/CRAC polypeptide, or a fragment thereof, also can be used to isolate naturally occurring, polypeptide binding partners which may associate with the SOC/CRAC polypeptide in the membrane of a cell. Isolation of binding partners may be performed
15 according to well-known methods. For example, isolated SOC/CRAC polypeptides can be attached to a substrate, and then a solution suspected of containing an SOC/CRAC binding partner may be applied to the substrate. If the binding partner for SOC/CRAC polypeptides is present in the solution, then it will bind to the substrate-bound SOC/CRAC polypeptide. The binding partner then may be isolated. Other proteins which are binding partners for
20 SOC/CRAC, may be isolated by similar methods without undue experimentation.

The invention also provides novel kits which could be used to measure the levels of the nucleic acids of the invention, expression products of the invention or anti-SOC/CRAC antibodies. In the case of nucleic acid detection, pairs of primers for amplifying SOC/CRAC nucleic acids can be included. The preferred kits would include controls such as known
25 amounts of nucleic acid probes, SOC/CRAC epitopes (such as SOC/CRAC expression products) or anti-SOC/CRAC antibodies, as well as instructions or other printed material. In certain embodiments the printed material can characterize risk of developing a disorder that is characterized by aberrant SOC/CRAC polypeptide expression based upon the outcome of the assay. The reagents may be packaged in containers and/or coated on wells in predetermined
30 amounts, and the kits may include standard materials such as labeled immunological reagents (such as labeled anti-IgG antibodies) and the like. One kit is a packaged polystyrene microtiter plate coated with a SOC/CRAC polypeptide and a container containing labeled anti-human IgG antibodies. A well of the plate is contacted with, for example, serum, washed

and then contacted with the anti-IgG antibody. The label is then detected. A kit embodying features of the present invention is comprised of the following major elements: packaging an agent of the invention, a control agent, and instructions. Packaging is a box-like structure for holding a vial (or number of vials) containing an agent of the invention. a vial (or number of
5 vials) containing a control agent, and instructions. Individuals skilled in the art can readily modify packaging to suit individual needs.

Another aspect of the invention is a method for determining the level of SOC/CRAC expression in a subject. As used herein, a subject is a human, non-human primate, cow, horse, pig, sheep, goat, dog, cat or rodent. In all embodiments, human subjects are preferred.
10 Expression is defined either as SOC/CRAC mRNA expression or SOC/CRAC polypeptide expression. Various methods can be used to measure expression. Preferred embodiments of the invention include PCR and Northern blotting for measuring mRNA expression, and monoclonal or polyclonal SOC/CRAC antisera as reagents to measure SOC/CRAC polypeptide expression. In certain embodiments, test samples such as biopsy samples, and
15 biological fluids such as blood, are used as test samples. SOC/CRAC expression in a test sample of a subject is compared to SOC/CRAC expression in control sample to, e.g., assess the presence or absence or stage of a proliferative disorder (e.g., a lymphocyte proliferative disorder) in a subject.

SOC/CRAC polypeptides preferably are produced recombinantly, although such
20 polypeptides may be isolated from biological extracts. Recombinantly produced SOC/CRAC polypeptides include chimeric proteins comprising a fusion of a SOC/CRAC protein with another polypeptide, e.g., a polypeptide capable of providing or enhancing protein-protein binding, sequence specific nucleic acid binding (such as GAL4), enhancing stability of the SOC/CRAC polypeptide under assay conditions, or providing a detectable moiety, such as
25 green fluorescent protein. A polypeptide fused to a SOC/CRAC polypeptide or fragment may also provide means of readily detecting the fusion protein, e.g., by immunological recognition or by fluorescent labeling.

The invention is also useful in the generation of transgenic non-human animals. As used herein, "transgenic non-human animals" includes non-human animals having one or
30 more exogenous nucleic acid molecules incorporated in germ line cells and/or somatic cells. Thus the transgenic animal include "knockout" animals having a homozygous or heterozygous gene disruption by homologous recombination, animals having episomal or chromosomally incorporated expression vectors, etc. Knockout animals can be prepared by

homologous recombination using embryonic stem cells as is well known in the art. The recombination may be facilitated using, for example, the cre/lox system or other recombinase systems known to one of ordinary skill in the art. In certain embodiments, the recombinase system itself is expressed conditionally, for example, in certain tissues or cell types, at certain embryonic or post-embryonic developmental stages, inducibly by the addition of a compound which increases or decreases expression, and the like. In general, the conditional expression vectors used in such systems use a variety of promoters which confer the desired gene expression pattern (e.g., temporal or spatial). Conditional promoters also can be operably linked to SOC/CRAC nucleic acid molecules to increase expression of SOC/CRAC in a regulated or conditional manner. *Trans*-acting negative regulators of SOC/CRAC calcium channel activity or expression also can be operably linked to a conditional promoter as described above. Such *trans*-acting regulators include antisense SOC/CRAC nucleic acids molecules, nucleic acid molecules which encode dominant negative SOC/CRAC molecules, ribozyme molecules specific for SOC/CRAC nucleic acids, and the like. The transgenic non-human animals are useful in experiments directed toward testing biochemical or physiological effects of diagnostics or therapeutics for conditions characterized by increased or decreased SOC/CRAC expression. Other uses will be apparent to one of ordinary skill in the art.

The invention further provides efficient methods of identifying agents or lead compounds for agents active at the level of a SOC/CRAC polypeptide (e.g., a SOC/CRAC polypeptide) or SOC/CRAC fragment dependent cellular function. In particular, such functions include interaction with other polypeptides or fragments thereof, and selective binding to certain molecules (e.g., agonists and antagonists). Generally, the screening methods involve assaying for compounds which interfere with SOC/CRAC calcium channel activity, although compounds which enhance SOC/CRAC calcium channel activity also can be assayed using the screening methods. Such methods are adaptable to automated, high throughput screening of compounds. The target therapeutic indications for pharmacological agents detected by the screening methods are limited only in that the target cellular function be subject to modulation by alteration of the formation of a complex comprising a SOC/CRAC polypeptide or fragment thereof and one or more SOC/CRAC binding targets. Target indications include cellular processes modulated by SOC/CRAC such as Ca^{2+} fluxing, and affected by SOC/CRAC ability to form complexes with other molecules and polypeptides as, for example, may be present in the cell membrane.

A wide variety of assays for pharmacological agents are provided, including, expression assays, labeled *in vitro* protein-protein binding assays, electrophoretic mobility shift assays, immunoassays, cell-based assays such as calcium transport assays, etc. For example, two-hybrid screens are used to rapidly examine the effect of transfected nucleic acids on the intracellular binding of SOC/CRAC or SOC/CRAC fragments to specific intracellular targets (e.g. a tyrosine kinase). The transfected nucleic acids can encode, for example, combinatorial peptide libraries or cDNA libraries. Convenient reagents for such assays, e.g., GAL4 fusion proteins, are known in the art. An exemplary cell-based assay involves transfecting a cell with a nucleic acid encoding a SOC/CRAC polypeptide fused to a GAL4 DNA binding domain and a nucleic acid encoding a reporter gene operably linked to a gene expression regulatory region, such as one or more GAL4 binding sites. Activation of reporter gene transcription occurs when the SOC/CRAC and reporter fusion polypeptides bind such as to enable transcription of the reporter gene. Agents which modulate a SOC/CRAC polypeptide mediated cell function are then detected through a change in the expression of reporter gene. Methods for determining changes in the expression of a reporter gene are known in the art.

In an expression system, for example, a SOC/CRAC polypeptide is attached to a membrane, the membrane preferably separating two fluid environments and being otherwise not permeable to Ca^{2+} . Such separation is preferred so that a change in Ca^{2+} concentration on either side of the membrane is mediated only through the attached SOC/CRAC polypeptide. Preferably, a SOC/CRAC polypeptide is expressed in an intact cell and is present on the cell-membrane (as in physiologic conditions). The cell expressing the SOC/CRAC polypeptide is preferably a eukaryotic cell, and the SOC/CRAC polypeptide is preferably recombinantly expressed, although cells naturally expressing a SOC/CRAC polypeptide may also be used. Synthetic membranes, however, containing SOC/CRAC polypeptides may also be used. See, e.g., K. Kiselyov, et al., Functional interaction between InsP3 receptors and store-operated Htrp3 channels, Nature 396, 478-82 (1998).

The cell expressing the SOC/CRAC polypeptide is incubated under conditions which, in the absence of the candidate agent, permit calcium flux into the cell and allow detection of a reference calcium concentration. For example, depletion of intracellular calcium stores with thapsigargin or other agents (Putney, J.W. Jr., in Capacitative Calcium Entry, R.G. Landes Co. and Chapman & Hall, 1997) would produce a given level of SOC/CRAC channel activation and a given reference calcium concentration. Detection of a decrease in the

foregoing activities (i.e., a decrease in the intracellular calcium concentration) relative to the reference calcium concentration indicates that the candidate agent is a lead compound for an agent to inhibit SOC/CRAC calcium channel activity. Preferred SOC/CRAC polypeptides include the polypeptides of claim 15.

5 SOC/CRAC fragments used in the methods, when not produced by a transfected nucleic acid are added to an assay mixture as an isolated polypeptide. SOC/CRAC polypeptides preferably are produced recombinantly, although such polypeptides may be isolated from biological extracts or chemically synthesized. Recombinantly produced SOC/CRAC polypeptides include chimeric proteins comprising a fusion of a SOC/CRAC
10 protein with another polypeptide, e.g., a polypeptide capable of providing or enhancing protein-protein binding, sequence specific nucleic acid binding (such as GAL4), enhancing stability of the SOC/CRAC polypeptide under assay conditions, or providing a detectable moiety, such as green fluorescent protein or Flag epitope.

The assay mixture is comprised of a SOC/CRAC polypeptide binding target
15 (candidate agent) capable of interacting with a SOC/CRAC polypeptide. While natural SOC/CRAC binding targets may be used, it is frequently preferred to use portions (e.g., peptides or nucleic acid fragments) or analogs (i.e., agents which mimic the SOC/CRAC binding properties of the natural binding target for purposes of the assay) of the SOC/CRAC binding target so long as the portion or analog provides binding affinity and avidity to the
20 SOC/CRAC polypeptide (or fragment thereof) measurable in the assay.

The assay mixture also comprises a candidate agent (binding target, e.g., agonist/antagonist). Typically, a plurality of assay mixtures are run in parallel with different agent concentrations to obtain a different response to the various concentrations. Typically, one of these concentrations serves as a negative control, i.e., at zero concentration of agent or
25 at a concentration of agent below the limits of assay detection. Candidate agents encompass numerous chemical classes, although typically they are organic compounds. Preferably, the candidate agents are small organic compounds, i.e., those having a molecular weight of more than 50 yet less than about 2500, preferably less than about 1000 and, more preferably, less than about 500. Candidate agents comprise functional chemical groups necessary for
30 structural interactions with polypeptides and/or nucleic acids, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups and more preferably at least three of the functional chemical groups. The candidate agents can comprise cyclic carbon or heterocyclic structure and/or aromatic or

-37-

polyaromatic structures substituted with one or more of the above-identified functional groups. Candidate agents also can be biomolecules such as peptides, saccharides, fatty acids, sterols, isoprenoids, purines, pyrimidines, derivatives or structural analogs of the above, or combinations thereof and the like. Where the agent is a nucleic acid, the agent typically is a DNA or RNA molecule, although modified nucleic acids as defined herein are also contemplated.

Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides, synthetic organic combinatorial libraries, phage display libraries of random peptides, and the like. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural and synthetically produced libraries and compounds can be readily modified through conventional chemical, physical, and biochemical means. Further, known agents may be subjected to directed or random chemical modifications such as acylation, alkylation, esterification, amidification, etc. to produce structural analogs of the agents. Non-SOC/CRAC calcium channel agonists and antagonists, for example, include agents such as dihydropyridines (DHPs), phenylalkylamines, omega conotoxin (omega-CgTx) and pyrazonoylguanidines.

A variety of other reagents also can be included in the mixture. These include reagents such as salts, buffers, neutral proteins (e.g., albumin), detergents, etc. which may be used to facilitate optimal protein-protein, protein-nucleic acid, and/or protein/membrane component binding association. Such a reagent may also reduce non-specific or background interactions of the reaction components. Other reagents that improve the efficiency of the assay such as protease, inhibitors, nuclease inhibitors, antimicrobial agents, and the like may also be used.

The mixture of the foregoing assay materials is incubated under conditions whereby, but for the presence of the candidate agent, the SOC/CRAC polypeptide specifically binds the cellular binding target, a portion thereof or analog thereof. The order of addition of components, incubation temperature, time of incubation, and other perimeters of the assay may be readily determined. Such experimentation merely involves optimization of the assay parameters, not the fundamental composition of the assay. Incubation temperatures typically

are between 4°C and 40°C. Incubation times preferably are minimized to facilitate rapid, high throughput screening, and typically are between 0.1 and 10 hours.

After incubation, the presence or absence of specific binding between the SOC/CRAC polypeptide and one or more binding targets is detected by any convenient method available to the user. For cell free binding type assays, a separation step is often used to separate bound from unbound components. The separation step may be accomplished in a variety of ways. Conveniently, at least one of the components is immobilized on a solid substrate, from which the unbound components may be easily separated. The solid substrate can be made of a wide variety of materials and in a wide variety of shapes, e.g., microtiter plate, microbead, dipstick, resin particle, etc. The substrate preferably is chosen to maximum signal to noise ratios, primarily to minimize background binding, as well as for ease of separation and cost.

Separation may be effected for example, by removing a bead or dipstick from a reservoir, emptying or diluting a reservoir such as a microtiter plate well, rinsing a bead, particle, chromatographic column or filter with a wash solution or solvent. The separation step preferably includes multiple rinses or washes. For example, when the solid substrate is a microtiter plate, the wells may be washed several times with a washing solution, which typically includes those components of the incubation mixture that do not participate in specific bindings such as salts, buffer, detergent, non-specific protein, etc. Where the solid substrate is a magnetic bead, the beads may be washed one or more times with a washing solution and isolated using a magnet.

Detection may be effected in any convenient way for cell-based assays such as two- or three-hybrid screens. The transcript resulting from a reporter gene transcription assay of SOC/CRAC polypeptide interacting with a target molecule typically encodes a directly or indirectly detectable product, e.g., β -galactosidase activity, luciferase activity, and the like. For cell-free binding assays, one of the components usually comprises, or is coupled to, a detectable label. A wide variety of labels can be used, such as those that provide direct detection (e.g., radioactivity, luminescence, optical or electron density, etc.) or indirect detection (e.g., epitope tag such as the FLAG epitope, enzyme tag such as horseradish peroxidase, etc.). The label may be bound to a SOC/CRAC binding partner, or incorporated into the structure of the binding partner.

A variety of methods may be used to detect the label, depending on the nature of the label and other assay components. For example, the label may be detected while bound to the solid substrate or subsequent to separation from the solid substrate. Labels may be directly

detected through optical or electron density, radioactive emissions, nonradiative energy transfers, etc. or indirectly detected with antibody conjugates, strepavidin-biotin conjugates, etc. Methods for detecting the labels are well known in the art.

Of particular importance in any of the foregoing assays and binding studies is the use
5 of a specific sequence motif identified in the SOC-2/CRAC-1 polypeptide sequence as a kinase catalytic domain. According to the invention, amino acids 999-1180 of the SOC-2/CRAC-1 polypeptide (SEQ ID NO:24) (or a fragment thereof), show a localized homology with the catalytic domains of eukaryotic elongation factor-2 kinase (eEF-2 kinase, GenBank
10 Acc. no. U93850) and *Dictyostelium* myocin heavy chain kinase A (MHCK A, GenBank Acc. no. U16856), as disclosed in Ryazanov AG, et al., *Proc Natl Acad Sci U S A*, 1997, 94(10):4884-4889. Therefore, according to the invention, a method for identifying agents useful in the modulation of SOC/CRAC polypeptide kinase activity is provided. The method involves contacting a SOC/CRAC polypeptide with kinase activity, that includes, for example, amino acids 999-1180 of the SOC-2/CRAC-1 polypeptide (SEQ ID NO:24) with a
15 candidate agent suspected of modulating SOC/CRAC kinase activity, under conditions sufficient to allow the candidate agent to interact with the SOC/CRAC polypeptide and modulate its kinase activity; detecting a kinase activity associated with the SOC/CRAC polypeptide in the presence of the candidate agent; and comparing the kinase activity in the previous step with a control kinase activity of a SOC/CRAC polypeptide in the absence of the
20 candidate agent to determine whether the candidate agent modulates (increases or decreases) SOC/CRAC kinase activity. Other controls for kinase activity can also be performed at the same time, for example, by utilizing eEF-2 kinase and/or *Dictyostelium* MHC Kinase A, in a similar manner to the SOC/CRAC member. Methods for performing such kinase activity assays are well known in the art.

25 The invention thus provides SOC/CRAC-specific binding agents, methods of identifying and making such agents, and their use in diagnosis, therapy and pharmaceutical development. For example, SOC/CRAC-specific agents are useful in a variety of diagnostic and therapeutic applications, especially where disease or disease prognosis is associated with altered SOC/CRAC and SOC/CRAC calcium channel fluxing characteristics. Novel
30 SOC/CRAC-specific binding agents include SOC/CRAC-specific antibodies and other natural intracellular and extracellular binding agents identified with assays such as two hybrid screens, and non-natural intracellular and extracellular binding agents identified in screens of chemical libraries and the like.

In general, the specificity of SOC/CRAC binding to a specific molecule is determined by binding equilibrium constants. Targets which are capable of selectively binding a SOC/CRAC polypeptide preferably have binding equilibrium constants of at least about 10^7 M^{-1} , more preferably at least about 10^8 M^{-1} , and most preferably at least about 10^9 M^{-1} . The wide variety of cell based and cell free assays may be used to demonstrate SOC/CRAC-specific binding. Cell based assays include one, two and three hybrid screens, assays in which SOC/CRAC-mediated transcription is inhibited or increased, etc. Cell free assays include SOC/CRAC-protein binding assays, immunoassays, etc. Other assays useful for screening agents which bind SOC/CRAC polypeptides include fluorescence resonance energy transfer (FRET), and electrophoretic mobility shift analysis (EMSA).

Various techniques may be employed for introducing nucleic acids of the invention into cells, depending on whether the nucleic acids are introduced *in vitro* or *in vivo* in a host. Such techniques include transfection of nucleic acid- $CaPO_4$ precipitates, transfection of nucleic acids associated with DEAE, transfection with a retrovirus including the nucleic acid of interest, liposome mediated transfection, and the like. For certain uses, it is preferred to target the nucleic acid to particular cells. In such instances, a vehicle used for delivering a nucleic acid of the invention into a cell (e.g., a retrovirus, or other virus; a liposome) can have a targeting molecule attached thereto. For example, a molecule such as an antibody specific for a surface membrane protein on the target cell or a ligand for a receptor on the target cell can be bound to or incorporated within the nucleic acid delivery vehicle. For example, where liposomes are employed to deliver the nucleic acids of the invention, proteins which bind to a surface membrane protein associated with endocytosis may be incorporated into the liposome formulation for targeting and/or to facilitate uptake. Such proteins include capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half life, and the like. Polymeric delivery systems also have been used successfully to deliver nucleic acids into cells, as is known by those skilled in the art. Such systems even permit oral delivery of nucleic acids.

Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the anti-inflammatory agent, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer base systems such as poly(lactide-glycolide), copolyoxalates, polycaprolactones,

polyesteramides, polyorthoesters, polyhydroxybutyric acid, and polyanhydrides. Microcapsules of the foregoing polymers containing drugs are described in, for example, U.S. Patent 5,075,109. Delivery systems also include non-polymer systems that are: lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono- di- and tri-glycerides; hydrogel release systems; sylastic systems; peptide based systems; wax coatings; compressed tablets using conventional binders and excipients; partially fused implants; and the like. Specific examples include, but are not limited to: (a) erosional systems in which an agent of the invention is contained in a form within a matrix such as those described in U.S. Patent Nos. 4,452,775, 4,675,189, and 5,736,152, and (b) diffusional systems in which an active component permeates at a controlled rate from a polymer such as described in U.S. Patent Nos. 3,854,480, 5,133,974 and 5,407,686. In addition, pump-based hardware delivery systems can be used, some of which are adapted for implantation.

Use of a long-term sustained release implant may be particularly suitable for treatment of chronic conditions. Long-term release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 30 days, and preferably 60 days. Long-term sustained release implants are well-known to those of ordinary skill in the art and include some of the release systems described above.

The invention also contemplates gene therapy. The procedure for performing *ex vivo* gene therapy is outlined in U.S. Patent 5,399,346 and in exhibits submitted in the file history of that patent, all of which are publicly available documents. In general, it involves introduction *in vitro* of a functional copy of a gene into a cell(s) of a subject which contains a defective copy of the gene, and returning the genetically engineered cell(s) to the subject. The functional copy of the gene is under operable control of regulatory elements which permit expression of the gene in the genetically engineered cell(s). Numerous transfection and transduction techniques as well as appropriate expression vectors are well known to those of ordinary skill in the art, some of which are described in PCT application WO95/00654. *In vivo* gene therapy using vectors such as adenovirus, retroviruses, herpes virus, and targeted liposomes also is contemplated according to the invention. See, e.g., U.S. Patent Nos. 5,670,488, entitled "Adenovirus Vector for Gene Therapy", issued to Gregory et al., and 5,672,344, entitled "Viral-Mediated Gene Transfer System", issued to Kelley et al.

The invention will be more fully understood by reference to the following examples. These examples, however, are merely intended to illustrate the embodiments of the invention and are not to be construed to limit the scope of the invention.

Examples

5 As an initial approach to identifying SOC/CRAC channels, we considered publicly available data and hypothesized that the following characteristics are likely to be exhibited by SOC/CRAC calcium channels: i) SOC/CRAC calcium channels would be integral membrane proteins related (probably distantly) to one of the known calcium channel families (e.g. voltage gated, ligand gated, Trp), and therefore should have a pore region formed by a tetramer of 6-7 transmembrane (TM) regions; ii) high calcium selectivity was likely to come at the price of complexity, and therefore these were likely to be large proteins; iii) the high calcium selectivity of this type of channel was likely to be useful and, therefore, highly conserved; and iv) these channels should be expressed in one or more types of lymphocytes, since ICRAC is best defined in those cell types. Since the full genome of the nematode *C. elegans* is nearing completion, and IP3-dependent calcium signals have recently been shown to be required for one or more aspects of *C. elegans* development, we took the set of proteins encoded by this genome (at the time this search was initiated WORMPEP14 was the available predicted protein set) and began searching for proteins which fit the criteria above. This search began by proceeding in alphabetical order through WORMPEP14 and arbitrarily excluding all proteins below approximately 1000 amino acids in size, followed by focusing on remaining proteins with clear TM spanning regions similar to those of other calcium channels. We stopped this screen on encountering a protein designated C05C12.3, a predicted protein of 1816 amino acids (SEQ ID NO:13). C05C12.3 was notable because its central pore region had some sequence similarity to but was clearly distinct from members of the Trp family of calcium channels, and the hydrophobicity plot of this region showed a characteristically wide spacing between the fifth and sixth TM regions for the amino acid residues which are thought to line the channel pore region and mediate the calcium selectivity of the channels. In addition, it lacked any ankyrin repeats in the region amino-terminal to its pore region, further distinguishing it from other Trp family proteins.

30 We then used C05C12.3 for BLAST alignment screening of the rest of the *C. elegans* genome and also mammalian databases for homologous proteins, revealing two other *C. elegans* homologues (SEQ ID NO:14 and SEQ ID NO:15), and also a recently cloned mammalian protein named melastatin-1 (MLSN-1/SOC-1, SEQ ID NOs:9 and 10, and

GenBank Acc. No. AF071787). Using these sequences, we subsequently performed an exhaustive screening of publicly accessible EST databases in search of lymphocyte homologues, but were unsuccessful in detecting any homologous transcripts in any lymphocyte lines. Since MLSN-1 (SEQ ID NOs:9 and 10) was expressed exclusively in melanocytes and retina by Northern blot hybridization and by EST database searching, there was no evidence that this type of channel was expressed in the type of cell in which ICRAC-like currents were best defined. Subsequent BLAST searches picked up mouse EST sequence AI098310 (SEQ ID NO:22) from a monocyte cell line. The I.M.A.G.E. consortium clone containing the above-identified EST was then purchased from ATCC (clone ID. 1312756, Manassas, VA) and was further characterized. Using other portions of this sequence in EST searches, we subsequently picked up similar sequences in human B-cells (SEQ ID NOs:20 and 21), and other cell types as well (SEQ ID NOs: 11, 12, 16, 17, 18, and 19). Most of these sequences were subsequently identified to be part of the 3'-UTR or of the carboxy terminal region of the proteins, which are not readily identifiable as Trp channels, providing an explanation for the art's inability to detect any type of Trp related transcripts in lymphocytes. Partial sequences from the 5' and/or 3' ends of the above identified clones were then used to screen leukocyte and kidney cDNA libraries to extend the original sequences more toward the 5' and/or 3' ends.

In view of the foregoing, it was concluded that channels of this type were expressed in many types of lymphocytes, and therefore were members of a new family of SOC/CRAC calcium channels.

Experimental Procedures Screening of the cDNA libraries

Leukocyte and kidney cDNA libraries from Life Technologies (Gaithersburg, MD) were screened using the Gene Trapper II methodology (Life Technologies) according to manufacturer's recommendation, using the inserts of I.M.A.G.E. clone ID nos. 1312756 and 1076485 from ATCC (Manassas, VA), under stringent hybridization conditions. Using standard methodology (*Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York), individual cDNA clones were subjected to 3-4 rounds of amplification and purification under the same hybridization conditions.

After excision from the vector and subcloning of inserts into the plasmid forms, several clones were sequenced by the Beth Israel Deaconess Medical Center's Automated

Sequencing Facility. Molecular biological techniques such as restriction enzyme treatment, subcloning, DNA extraction, bacterial culture and purification of DNA fragments were performed according to methods well known in the art. Computer analyses of protein and DNA sequences was done using "Assemblylign" (Oxford Molecular, Campbell, CA). Multiple
5 alignments of the SOC/CRAC family members were produced using the CLUSTAL facility of the MacVector program. Restriction endonucleases, expression vectors, and modifying enzymes were purchased from commercial sources (Gibco-BRL). Sequencing vectors for DNA were purchased from Stratagene (La Jolla, CA).

Once the first members of what appeared to be a novel family of calcium channel
10 receptors were identified and characterized, additional BLAST alignments were performed with the newly characterized nucleic acid sequences. An initial match was with genomic DNA fragment NH0332L11 (Genbank Acc. No. AC005538). Using this genomic sequence, promoters were designed and a number of cDNA libraries was surveyed by PCR. A prostate specific message was identified and characterized, leading to the isolation and
15 characterization of SOC-4/CRAC-3 (SEQ ID NOs: 31 and 32).

Functional Assays

Transient Expression of SOC/CRAC

In our initial transient expression experiments, we expressed or expect to express a SOC/CRAC molecule transiently in RBL-2H3 mast cells, Jurkat T cells, and A20
20 B-lymphocytes using both electroporation and vaccinia virus-driven expression, and measured the calcium influx produced by depletion of intracellular calcium stores with thapsigargin. Each of the foregoing techniques is well known to those of ordinary skill in the art and can be performed using various methods (see, e.g., Current Methods in Molecular Biology, eds. Ausubal, F.M., et al. 1987, Green Publishers and Wiley Interscience, N.Y.,
25 N.Y.). Exemplary methods are described herein.

Depletion of intracellular calcium stores is accomplished by treating the cells with 1 micromolar thapsigargin; alternative agents which function to deplete intracellular stores are described in by Putney, J.W. Jr., in Capacitative Calcium Entry, R.G. Landes Co. and Chapman & Hall, 1997 and include, for example, ionomycin, cyclopiazonic acid, and DBHQ.

30 Calcium influx is determined by measuring cytoplasmic calcium as indicated using the fura-2 fluorescent calcium indicator (see, e.g., G. Grynkiewicz, M. Poenie, R. Y. Tsien, A new generation of Ca²⁺ indicators with greatly improved fluorescence properties, J. Biol

Chem 260, 3440-50 (1985), and M. Poenie, R. Tsien, Fura-2: a powerful new tool for measuring and imaging $[Ca^{2+}]_i$ in single cells, Prog Clin Biol Res 210, 53-6 (1986)).

Patch Clamp Analysis and Determining Selectivity of SOC/CRAC

Patch clamp analysis of cells injected with SOC/CRAC cRNA is performed by using the general patch technique as described in Neher, E., "Ion channels for communication between and within cells", Science, 1992; 256:498-502. Specific techniques for applying the patch clamp analysis to RBL cells are described in Hoth, M., and Penner, R., "Depletion of intracellular calcium stores activates a calcium current in mast cells", Nature, 1992; 355:3535-3555. Additional protocols for applying the patch clamp technique to other cell types are described in Putney, J.W. Jr., in Capacitative Calcium Entry, R.G. Landes Co. and Chapman & Hall, 1997

An exemplary protocol for patch clamp analysis of SOC/CRAC molecule expressed in RBL-2H3 mast cells using a recombinant vaccinia virus is as follows. The currents elicited by store depletion are determined using the whole cell configuration (Neher, E., Science, 1992; 256:498-502). Currents in SOC/CRAC expressing cells are compared to currents in control cells expressing an irrelevant protein or a classic Trp family calcium channel known as VR1 (M. J. Caterina, et al., The capsaicin receptor: a heat-activated ion channel in the pain pathway [see comments], Nature 389, 816-24 (1997)) in order to assess the contribution of SOC/CRAC expression. In addition, the magnitude of whole cell currents in the presence of extracellular calcium (10 mM), barium (10 mM), or magnesium (10 mM) are compared to determine the relative permeability of the channels to each of these ions (Hoth, M., and Penner, R., Nature, 1992; 355:3535-3555) and, thereby, determine the ionic selectivity.

Pharmacologic Behavior of SOC/CRAC

For analysis of the pharmacologic behavior of a SOC/CRAC molecule, a SOC/CRAC molecule is expressed in RBL-2H3 mast cells using a recombinant vaccinia virus, and the degree of calcium influx elicited by store depletion is monitored using a bulk spectrofluorimeter or a fluorescence microscope and the calcium sensitive dye fura-2 (G. Grynkiewicz, M. Poenie, R. Y. Tsien, A new generation of Ca^{2+} indicators with greatly improved fluorescence properties, J Biol Chem 260, 3440-50 (1985) and M. Poenie, R. Tsien, Fura-2: a powerful new tool for measuring and imaging $[Ca^{2+}]_i$ in single cells, Prog Clin Biol Res 210, 53-6 (1986)). The level of cytoplasmic calcium in SOC/CRAC expressing cells is compared to the level achieved in control cells expressing an irrelevant protein or a classic Trp. family calcium channels known as VR1 (M. J. Caterina, et al., The

capsaicin receptor: a heat-activated ion channel in the pain pathway [see comments], Nature 389, 816-24 (1997)). These cells then are pre-incubated with the desired pharmacologic reagent, and again the response to store depletion is monitored. Comparison of the effect of depleting stores in SOC/CRAC expressing cells relative to controls in the presence or absence of the pharmacologic reagent is used to assess the ability of that reagent to modulate SOC/CRAC activity. Sphingosine is an exemplary molecule that can be used as pharmacologic reagents for pharmacologic characterization of SOC/CRAC calcium channels. See, e.g., Mathes, C., et al., Calcium release activated calcium current as a direct target for sphingosine, J Biol Chem 273(39):25020-25030 (1998). Other non-specific calcium channel inhibitors that can be used for this purpose include SKR96365 (Calbiochem) and Lanthanum.

Bulk Calcium Assays

Bulk calcium assays can be performed in a PTI Deltascan bulk spectrofluorometer using fura-2 as described in Scharenberg AM, et al., EMBO J, 1995, 14(14):3385-94.

Gene Targeting

The method (and reagents) described by Buerstedde JM et al, (Cell, 1991, Oct 4;67(1):179-88), was used to generate "knockouts" in cells. Briefly, part of the chicken SOC-2/CRAC-1 genomic sequence coding for the transmembrane region was cloned utilizing the human sequence as the probe in a chicken library screen. Chicken SOC-2/CRAC-1 clones were isolated and characterized using standard methodology. The putative exon and domain arrangement of the chicken SOC-2/CRAC-1, is depicted in Figure 1. The exons coding for TM5 (pore region) and TM6, were replaced with promoter/antibiotic cassettes (see Figure1). These targeting vectors were then used to target (and replace) the endogenous gene in DT-40 cells (chicken B lymphocyte cells).

Results

Example 1: Transient Expression of SOC/CRAC

In the above-identified cell lines and using both of the foregoing expression techniques, SOC/CRAC expression enhances thapsigargin-dependent influx. In addition, SOC/CRAC expression also enhances the amount of intracellular calcium stores. That this effect is likely due to SOC/CRAC acting as a plasma membrane calcium channel can be confirmed by producing an in-frame carboxy-terminal translational fusion with green fluorescent protein followed by confocal microscopy, revealing that SOC/CRAC is expressed predominantly as a plasma membrane calcium channel.

Example 2: Patch Clamp Analysis

The biophysical characteristics of SOC/CRAC enhanced currents when expressed in *Xenopus* oocytes are determined. SOC/CRAC cRNA injection is able to enhance thapsigargin-dependent whole cell currents. In addition, SOC/CRAC does not alter the reversal potential of these currents and the determination of the P_{Ca}/P_{Na} ratio shows that SOC/CRAC channels are highly calcium selective.

Example 3: *Pharmacologic Behavior of SOC/CRAC*

The pharmacologic behavior of SOC/CRAC is evaluated as described above. SOC/CRAC-enhanced influx is inhibited by sphingosine in a manner that is substantially the same as that of endogenous thapsigargin-dependent calcium influx.

Example 4: *Gene targeting*

Transfection of DT-40 cells with the foregoing targeting vectors, selection for antibiotic resistance, and screening, is collectively referred to, herein, as a round of targeting. For the first round of targeting SOC-2/CRAC-1, 18/24 clones with homologous recombination of the targeting construct into one of the endogenous SOC-2/CRAC-1 alleles were obtained. On the second round of targeting (in order to target the second allele and therefore generate a homozygous SOC-2/CRAC-1 mutant cell), 0/48 clones were obtained. These results indicate that a "null" SOC-2/CRAC-1 mutation is detrimental to DT-40 cells, and that SOC-2/CRAC-1 is required for cell viability.

Table I. Nucleotide Sequences with homologies to SOC/CRAC nucleic acids

Sequences with SEQ ID NOs and GenBank accession numbers:
SEQ ID NO:9, AB001535, AI226731, H18835, AA419592, AA261842, AA419407, AA592910, D86107, AI098310, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, AC005538, AA654650, AA370110, AA313170, AA493512, AI670079, AI671853.

Table II. Amino Acid Sequences with homologies to SOC/CRAC polypeptides

Sequences with SEQ ID NOs and GenBank accession numbers:
SEQ ID NO:10, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, AB001535, AA592910, D86107, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, NP003298, CAB00861, NP002411, CAA92726, CAB05572.

All references, patents, and patent documents disclosed herein are incorporated by reference herein in their entirety.

What is claimed is presented below and is followed by a Sequence Listing. We claim:

Claims

1. An isolated nucleic acid molecule, comprising:

(a) nucleic acid molecules which hybridize under stringent conditions to a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, and which code for a SOC/CRAC polypeptide;

(b) deletions, additions and substitutions of (a) which code for a respective SOC/CRAC polypeptide;

(c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) in codon sequence due to the degeneracy of the genetic code, and

(d) complements of (a), (b) or (c).

2. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:1.

3. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:27.

4. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:29.

5. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:31.

6. An isolated nucleic acid molecule selected from the group consisting of

(a) a unique fragment of a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:29, and SEQ ID NO:31,

(b) complements of (a),

provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to any sequence selected from a sequence group consisting of

(1) sequences having the SEQ. ID NOS. or GenBank accession numbers of Table I,

(2) complements of (1), and

(3) fragments of (1) and (2).

7. The isolated nucleic acid molecule of claim 6, wherein the sequence of contiguous nucleotides is selected from the group consisting of:

- (1) at least two contiguous nucleotides nonidentical to the sequence group,
- (2) at least three contiguous nucleotides nonidentical to the sequence group,
- (3) at least four contiguous nucleotides nonidentical to the sequence group,
- (4) at least five contiguous nucleotides nonidentical to the sequence group,
- (5) at least six contiguous nucleotides nonidentical to the sequence group,
- (6) at least seven contiguous nucleotides nonidentical to the sequence group.

8. The isolated nucleic acid molecule of claim 6, wherein the unique fragment has a size selected from the group consisting of at least: 8 nucleotides, 10 nucleotides, 12 nucleotides, 14 nucleotides, 16 nucleotides, 18 nucleotides, 20, nucleotides, 22 nucleotides, 24 nucleotides, 26 nucleotides, 28 nucleotides, 30 nucleotides, 50 nucleotides, 75 nucleotides, 100 nucleotides, and 200 nucleotides.

9. The isolated nucleic acid molecule of claim 6, wherein the molecule encodes a polypeptide which is immunogenic.

10. An expression vector comprising the isolated nucleic acid molecule of claims 1, 2, 3, 4, 5, 6, 7, 8, or 9 operably linked to a promoter.

11. A host cell transformed or transfected with the expression vector of claim 10.

12. An isolated polypeptide encoded by the isolated nucleic acid molecule according to anyone of claims 1 or 6, wherein the polypeptide comprises a SOC/CRAC polypeptide or a unique fragment thereof.

13. The isolated polypeptide of claim 12, wherein the isolated polypeptide is encoded by the isolated nucleic acid molecule of claim 2, 3, 4, or 5.

14. The isolated polypeptide of claim 13, wherein the isolated polypeptide comprises a polypeptide having the sequence of amino acids selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32.

15. An isolated polypeptide encoded by the isolated nucleic acid molecule of claim 1, 2, 3, 4, or 5, wherein the polypeptide, or unique fragment thereof is immunogenic.

16. An isolated binding polypeptide which binds selectively to a polypeptide encoded by the isolated nucleic acid molecule of claim 1, 2, 3, 4, or 5.

5 17. The isolated binding polypeptide of claim 16, wherein the isolated binding polypeptide binds to a polypeptide having the sequence of amino acids selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32.

10 18. The isolated binding polypeptide of claim 17, wherein the isolated binding polypeptide is an antibody or an antibody fragment selected from the group consisting of a Fab fragment, a F(ab)₂ fragment or a fragment including a CDR3 region selective for the polypeptide.

15 19. An isolated polypeptide, comprising a unique fragment of the polypeptide of claim 12 of sufficient length to represent a sequence unique within the human genome, provided that the fragment excludes a sequence of contiguous amino acids identified in Table II.

20. A method for isolating a SOC/CRAC molecule having SOC/CRAC calcium channel activity, comprising:

20 a) contacting a binding molecule that is a SOC/CRAC nucleic acid or a SOC/CRAC binding polypeptide with a sample containing one or more SOC/CRAC molecules, under conditions sufficient to form a complex of the SOC/CRAC nucleic acid or the SOC/CRAC binding polypeptide and the SOC/CRAC molecule;

b) detecting the presence of the complex;

c) isolating the SOC/CRAC molecule from the complex; and

25 d) determining whether the isolated SOC/CRAC molecule has SOC/CRAC calcium channel activity.

21. The method of claim 20, wherein the binding molecule is a SOC/CRAC nucleic acid.

22. The method of claim 20, wherein the binding molecule is a SOC/CRAC binding polypeptide.

23. The method of claim 21, wherein the SOC/CRAC nucleic acid comprises at least 14 nucleotides from any contiguous portion of a sequence of nucleotides selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31.

5 24. A method for identifying agents useful in the modulation of SOC/CRAC calcium channel activity, comprising:

a) contacting a SOC/CRAC polypeptide with a candidate agent suspected of modulating SOC/CRAC calcium channel activity, under conditions sufficient to allow the SOC/CRAC polypeptide to interact selectively with the candidate agent;

10 b) detecting a Ca^{2+} concentration associated with SOC/CRAC calcium channel activity of the SOC/CRAC polypeptide in the presence of the candidate agent; and

c) comparing the Ca^{2+} concentration of step (b) with a control Ca^{2+} concentration of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the candidate agent modulates SOC/CRAC calcium channel activity.

15

25. A method for determining the level of SOC/CRAC expression in a subject, comprising:

a) measuring the expression of SOC/CRAC in a test sample obtained from the subject, and

20 b) comparing the measured expression of SOC/CRAC in the test sample to the expression of the SOC/CRAC polypeptide in a control to determine the level of SOC/CRAC expression in the subject.

25

26. The method of claim 25, wherein the expression of SOC/CRAC in (b) is SOC/CRAC mRNA expression.

27. The method of claim 25, wherein the expression of SOC/CRAC in (b) is SOC/CRAC polypeptide expression.

28. The method of claim 25, wherein the test sample is tissue.

29. The method of claim 25, wherein the test sample is a biological fluid.

30. The method of claim 26, wherein SOC/CRAC mRNA expression is measured using the Polymerase Chain Reaction (PCR).

31. The method of claim 26, wherein SOC/CRAC mRNA expression is measured using a method selected from the group consisting of northern blotting, monoclonal antisera to SOC/CRAC and polyclonal antisera to SOC/CRAC.

32. A kit, comprising a package containing:

an agent that selectively binds to the isolated nucleic acid of claim 1 or an expression product thereof, and

a control for comparing to a measured value of binding of said agent to said isolated nucleic acid of claim 1 or expression product thereof.

33. The kit of claim 32, wherein the control comprises an epitope of the expression product of the nucleic acid of claim 1.

34. A pharmaceutical composition comprising:

a pharmaceutically effective amount of an agent comprising of an isolated nucleic acid molecule of claim 1 or an expression product thereof, and

a pharmaceutically acceptable carrier.

35. The pharmaceutical composition of claim 34, wherein the agent is an expression product of the isolated nucleic acid molecule of claim 1.

36. A method for identifying agents useful in the modulation of a SOC/CRAC polypeptide kinase activity, comprising:

a) contacting a SOC/CRAC polypeptide with kinase activity with a candidate agent suspected of modulating SOC/CRAC kinase activity, under conditions sufficient to allow the candidate agent to interact with the SOC/CRAC polypeptide and modulate its kinase activity;

b) detecting a kinase activity associated with the SOC/CRAC polypeptide in the presence of the candidate agent; and

c) comparing the kinase activity of step (b) with a control kinase activity of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the candidate agent modulates SOC/CRAC kinase activity.

37. The method of claim 36, wherein the SOC/CRAC polypeptide comprises amino acids 999-1180 of the sequence represented as SEQ ID NO:24, or a fragment thereof that retains the kinase activity.

1/1

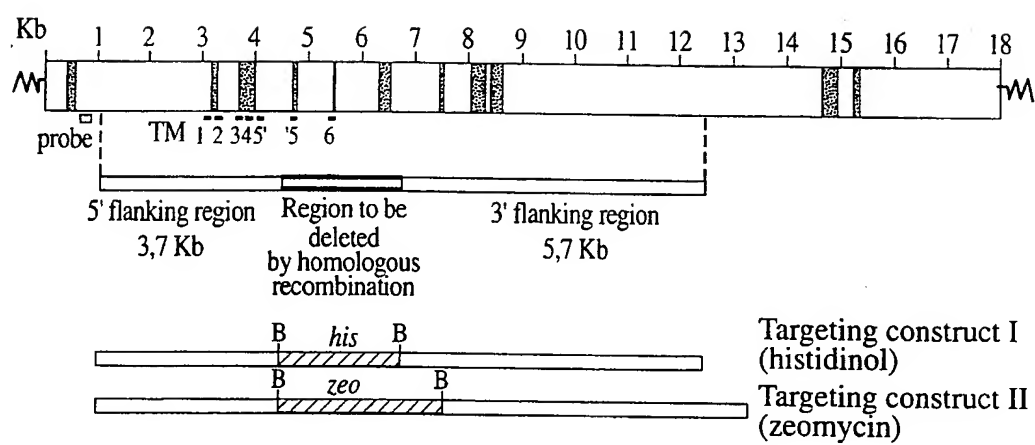


Fig. 1

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Scharenberg, Andrew

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His	Glu	Lys	Pro	Val	Leu	Pro	Pro	Pro	Leu	Ile	Ile	Leu	Ser	His	Ile
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Gln	Leu	His	Lys	Lys	Ile	Ile	Thr	Ile	Ile	Arg	Phe	Ser	Asn	Trp	Pro
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			20				25					30			
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-5-

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-6-

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<211> 475

<212> PRT

<213> Mus Musculus

<400> 8

-7-

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Val His Gly Gly Leu Gln Asn Phe Glu Met Gln Pro Lys Leu Lys Gln
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Val Phe Gly Lys Gly Leu Ile Lys Ala Ala Met Thr Thr Gly Ala Trp
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-10-

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-11-

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-12-

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<210> 12

<211> 1503

-15-

<212> PRT

<213> Homo Sapiens

<400> 12

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Leu Arg Arg Ser Asn Ser Ser Leu Phe Lys Ser Trp Arg Leu Gln Cys
 35          40          45
Pro Phe Gly Asn Asn Asp Lys Gln Glu Ser Leu Ser Ser Trp Ile Pro
 50          55          60
Glu Asn Ile Lys Lys Lys Glu Cys Val Tyr Phe Val Glu Ser Ser Lys
 65          70          75          80
Leu Ser Asp Ala Gly Lys Val Val Cys Gln Cys Gly Tyr Thr His Glu
          85          90          95
Gln His Leu Glu Glu Ala Thr Lys Pro His Thr Phe Gln Gly Thr Gln
          100          105          110
Trp Asp Pro Lys Lys His Val Gln Glu Met Pro Thr Asp Ala Phe Gly
          115          120          125
Asp Ile Val Phe Thr Gly Leu Ser Gln Lys Val Lys Lys Tyr Val Arg
          130          135          140
Val Ser Gln Asp Thr Pro Ser Ser Val Ile Tyr His Leu Met Thr Gln
          145          150          155          160
His Trp Gly Leu Asp Val Pro Asn Leu Leu Ile Ser Val Thr Gly Gly
          165          170          175
Ala Lys Asn Phe Asn Met Lys Pro Arg Leu Lys Ser Ile Phe Arg Arg
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Gly Leu Val Lys Val Ala Gln Thr Thr Gly Ala Trp Ile Ile Thr Gly
          195          200          205
Gly Ser His Thr Gly Val Met Lys Gln Val Gly Glu Ala Val Arg Asp
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Phe Ser Leu Ser Ser Ser Tyr Lys Glu Gly Glu Leu Ile Thr Ile Gly
          225          230          235          240
Val Ala Thr Trp Gly Thr Val His Arg Arg Glu Gly Leu Ile His Pro
          245          250          255
Thr Gly Ser Phe Pro Ala Glu Tyr Ile Leu Asp Glu Asp Gly Gln Gly
          260          265          270
Asn Leu Thr Cys Leu Asp Ser Asn His Ser His Phe Ile Leu Val Asp
          275          280          285
Asp Gly Thr His Gly Gln Tyr Gly Val Glu Ile Pro Leu Arg Thr Arg
          290          295          300
Leu Glu Lys Phe Ile Ser Glu Gln Thr Lys Glu Arg Gly Gly Val Ala
          305          310          315          320
Ile Lys Ile Pro Ile Val Cys Val Val Leu Glu Gly Gly Pro Gly Thr
          325          330          335
Leu His Thr Ile Asp Asn Ala Thr Thr Asn Gly Thr Pro Cys Val Val
          340          345          350
Val Glu Gly Ser Gly Arg Val Ala Asp Val Ile Ala Gln Val Ala Asn
          355          360          365
Leu Pro Val Ser Asp Ile Thr Ile Ser Leu Ile Gln Gln Lys Leu Ser
          370          375          380
Val Phe Phe Gln Glu Met Phe Glu Thr Phe Thr Glu Ser Arg Ile Val
          385          390          395          400
Glu Trp Thr Lys Lys Ile Gln Asp Ile Val Arg Arg Arg Gln Leu Leu
          405          410          415
Thr Val Phe Arg Glu Gly Lys Asp Gly Gln Gln Asp Val Asp Val Ala
          420          425          430
Ile Leu Gln Ala Leu Leu Lys Ala Ser Arg Ser Gln Asp His Phe Gly
          435          440          445

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-16-

His	Glu	Asn	Trp	Asp	His	Gln	Leu	Lys	Leu	Ala	Val	Ala	Trp	Asn	Arg
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Pro	Ser	Asp	Leu	His	Pro	Thr	Met	Thr	Ala	Ala	Leu	Ile	Ser	Asn	Lys
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Pro	Glu	Phe	Val	Lys	Leu	Phe	Leu	Glu	Asn	Gly	Val	Gln	Leu	Lys	Glu
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Phe	Val	Thr	Trp	Asp	Thr	Leu	Leu	Tyr	Leu	Tyr	Glu	Asn	Leu	Asp	Pro
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Ser	Cys	Leu	Phe	His	Ser	Lys	Leu	Gln	Lys	Val	Leu	Val	Glu	Asp	Pro
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Glu	Arg	Pro	Ala	Cys	Ala	Pro	Ala	Ala	Pro	Arg	Leu	Gln	Met	His	His
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Val	Ala	Gln	Val	Leu	Arg	Glu	Leu	Leu	Gly	Asp	Phe	Thr	Gln	Pro	Leu
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Tyr	Pro	Arg	Pro	Arg	His	Asn	Asp	Arg	Leu	Arg	Leu	Leu	Leu	Pro	Val
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Pro	His	Val	Lys	Leu	Asn	Val	Gln	Gly	Val	Ser	Leu	Arg	Ser	Leu	Tyr
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Lys	Arg	Ser	Ser	Gly	His	Val	Thr	Phe	Thr	Met	Asp	Pro	Ile	Arg	Asp
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Leu	Leu	Ile	Trp	Ala	Ile	Val	Gln	Asn	Arg	Arg	Glu	Leu	Ala	Gly	Ile
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Ile	Trp	Ala	Gln	Ser	Gln	Asp	Cys	Ile	Ala	Ala	Ala	Leu	Ala	Cys	Ser
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Lys	Ile	Leu	Lys	Glu	Leu	Ser	Lys	Glu	Glu	Glu	Asp	Thr	Asp	Ser	Ser
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Glu	Glu	Met	Leu	Ala	Leu	Ala	Glu	Glu	Tyr	Glu	His	Arg	Ala	Ile	Gly
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Val	Phe	Thr	Glu	Cys	Tyr	Arg	Lys	Asp	Glu	Glu	Arg	Ala	Gln	Lys	Leu
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Leu	Thr	Arg	Val	Ser	Glu	Ala	Trp	Gly	Lys	Thr	Thr	Cys	Leu	Gln	Leu
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Ala	Leu	Glu	Ala	Lys	Asp	Met	Lys	Phe	Val	Ser	His	Gly	Gly	Ile	Gln
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Ala	Phe	Leu	Thr	Lys	Val	Trp	Trp	Gly	Gln	Leu	Ser	Val	Asp	Asn	Gly
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Leu	Trp	Arg	Val	Thr	Leu	Cys	Met	Leu	Ala	Phe	Pro	Leu	Leu	Leu	Thr
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Gly	Leu	Ile	Ser	Phe	Arg	Glu	Lys	Arg	Leu	Gln	Asp	Val	Gly	Thr	Pro
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Ala	Ala	Arg	Ala	Arg	Ala	Phe	Phe	Thr	Ala	Pro	Val	Val	Val	Phe	His
785					790					795					800
Leu	Asn	Ile	Leu	Ser	Tyr	Phe	Ala	Phe	Leu	Cys	Leu	Phe	Ala	Tyr	Val
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Leu	Met	Val	Asp	Phe	Gln	Pro	Val	Pro	Ser	Trp	Cys	Glu	Cys	Ala	Ile
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Tyr	Leu	Trp	Leu	Phe	Ser	Leu	Val	Cys	Glu	Glu	Met	Arg	Gln	Leu	Phe
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Tyr	Asp	Pro	Asp	Glu	Cys	Gly	Leu	Met	Lys	Lys	Ala	Ala	Leu	Tyr	Phe
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Ser	Asp	Phe	Trp	Asn	Lys	Leu	Asp	Val	Gly	Ala	Ile	Leu	Leu	Phe	Val
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Ala	Gly	Leu	Thr	Cys	Arg	Leu	Ile	Pro	Ala	Thr	Leu	Tyr	Pro	Gly	Arg
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Val	Ile	Leu	Ser	Leu	Asp	Phe	Ile	Leu	Phe	Cys	Leu	Arg	Leu	Met	His
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-17-

Arg Met Met Lys Asp Val Phe Phe Phe Leu Phe Leu Leu Ala Val Trp
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 Val Val Ser Phe Gly Val Ala Lys Gln Ala Ile Leu Ile His Asn Glu
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 Arg Arg Val Asp Trp Leu Phe Arg Gly Ala Val Tyr His Ser Tyr Leu
 965 970 975
 Thr Ile Phe Gly Gln Ile Pro Gly Tyr Ile Asp Gly Val Asn Phe Asn
 980 985 990
 Pro Glu His Cys Ser Pro Asn Gly Thr Asp Pro Tyr Lys Pro Lys Cys
 995 1000 1005
 Pro Glu Ser Asp Ala Thr Gln Gln Arg Pro Ala Phe Pro Glu Trp Leu
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 Thr Val Leu Leu Leu Cys Leu Tyr Leu Leu Phe Thr Asn Ile Leu Leu
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 Leu Asn Leu Leu Ile Ala Met Phe Asn Tyr Thr Phe Gln Gln Val Gln
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 Glu His Thr Asp Gln Ile Trp Lys Phe Gln Arg His Asp Leu Ile Glu
 1060 1065 1070
 Glu Tyr His Gly Arg Pro Ala Ala Pro Pro Pro Phe Ile Leu Leu Ser
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 His Leu Gln Leu Phe Ile Lys Arg Val Val Leu Lys Thr Pro Ala Lys
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 Arg His Lys Gln Leu Lys Asn Lys Leu Glu Lys Asn Glu Glu Ala Ala
 1105 1110 1115 112
 Leu Leu Ser Trp Glu Ile Tyr Leu Lys Glu Asn Tyr Leu Gln Asn Arg
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 1155 1160 1165
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 1170 1175 1180
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 Ala Ala Glu Glu Pro Asp Ala Glu Pro Gly Gly Arg Lys Lys Thr Glu
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 Glu Pro Gly Asp Ser Tyr His Val Asn Ala Arg His Leu Leu Tyr Pro
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 Asn Cys Pro Val Thr Arg Phe Pro Val Pro Asn Glu Lys Val Pro Trp
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 Glu Thr Glu Phe Leu Ile Tyr Asp Pro Pro Phe Tyr Thr Ala Glu Arg
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 Lys Asp Ala Ala Ala Met Asp Pro Met Gly Asp Thr Leu Glu Pro Leu
 1285 1290 1295
 Ser Thr Ile Gln Tyr Asn Val Val Asp Gly Leu Arg Asp Arg Arg Ser
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 Phe His Gly Pro Tyr Thr Val Gln Ala Gly Leu Pro Leu Asn Pro Met
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 1330 1335 1340
 Asn His Thr Leu Tyr Pro Met Val Thr Arg Trp Arg Arg Asn Glu Asp
 1345 1350 1355 136
 Gly Ala Ile Cys Arg Lys Ser Ile Lys Lys Met Leu Glu Val Leu Val
 1365 1370 1375
 Val Lys Leu Pro Leu Ser Glu His Trp Ala Leu Pro Gly Gly Ser Arg
 1380 1385 1390
 Glu Pro Gly Glu Met Leu Pro Arg Lys Leu Lys Arg Ile Leu Arg Gln
 1395 1400 1405

-18-

Glu His Trp Pro Ser Phe Glu Asn Leu Leu Lys Cys Gly Met Glu Val
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 Tyr Lys Gly Tyr Met Asp Asp Pro Arg Asn Thr Asp Asn Ala Trp Ile
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 Glu Thr Val Ala Val Ser Val His Phe Gln Asp Gln Asn Asp Val Glu
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 1460 1465 1470
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 Phe Phe Leu Thr Leu Ile Ala Gly Val Thr His Phe Tyr Phe Pro Glu
 50 55 60
 Lys Leu Leu Gly Lys Ser Glu Asn Leu Asp His Arg Tyr Gln Ser Ser
 65 70 75 80
 Glu Gln Lys Val Leu Ile Glu Trp Thr Glu Asn Lys Ala Val Ala Glu
 85 90 95
 Ser Leu Arg Ala Asn Ser Val Thr Val Glu Glu Asn Glu Ser Glu Arg
 100 105 110
 Glu Thr Glu Thr Gln Thr Lys Arg Arg Arg Lys Lys Gln Arg Ser Thr
 115 120 125
 Ser Ser Asp Lys Ala Pro Leu Asn Ser Ala Pro Arg His Val Gln Lys
 130 135 140
 Phe Asp Trp Lys Asp Met Leu His Leu Ala Asp Ile Ser Gly Arg Lys
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 Arg Gly Asn Ser Thr Thr Ser His Ser Gly His Ala Thr Arg Ala Gly
 165 170 175
 Ser Leu Lys Gly Lys Asn Trp Ile Glu Cys Arg Leu Lys Met Arg Gln
 180 185 190
 Cys Ser Tyr Phe Val Pro Ser Gln Arg Phe Ser Glu Arg Cys Gly Cys
 195 200 205
 Gly Lys Glu Arg Ser Lys His Thr Glu Glu Val Leu Glu Arg Ser Gln
 210 215 220
 Asn Lys Asn His Pro Leu Asn His Leu Thr Leu Pro Gly Ile His Glu
 225 230 235 240
 Val Asp Thr Thr Asp Ala Asp Ala Asp Asp Asn Glu Val Asn Leu Thr
 245 250 255
 Pro Gly Arg Trp Ser Ile Gln Ser His Thr Glu Ile Val Pro Thr Asp
 260 265 270
 Ala Tyr Gly Asn Ile Val Phe Glu Gly Thr Ala His His Ala Gln Tyr
 275 280 285
 Ala Arg Ile Ser Phe Asp Ser Asp Pro Arg Asp Ile Val His Leu Met
 290 295 300
 Met Lys Val Trp Lys Leu Lys Pro Pro Lys Leu Ile Ile Thr Ile Asn
 305 310 315 320
 Gly Gly Leu Thr Lys Phe Asp Leu Gln Pro Lys Leu Ala Arg Thr Phe

-19-

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Asp	Val	Leu	Leu	Ala	His	Ser	Met	Phe	Ile	Pro	Arg	Gly	Ser	Leu	Phe
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Ala	Ser	Trp	Gly	Met	Leu	Lys	Gln	Arg	Ser	Arg	Phe	Val	Gly	Lys	Asp
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Ser	Thr	Val	Thr	Tyr	Ala	Thr	Asn	Val	Phe	Asn	Asn	Thr	Arg	Leu	Lys
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Tyr	Leu	Ala	Gln	Gly	Asp	Lys	Lys	Arg	Ser	Ala	Ile	Pro	Leu	Val	Cys
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Ile	Val	Glu	Cys	Ser	Thr	Asn	Lys	Ser	Leu	Met	Thr	Ile	Phe	Arg	Leu
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Gly	Glu	Ser	Ser	Arg	Glu	Asp	Leu	Asp	His	Val	Ile	Met	Ser	Cys	Leu
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Thr	Glu	Trp	Thr	Thr	Gln	Asp	Leu	His	Asn	Ala	Met	Ile	Glu	Ala	Leu
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Ser	Asn	Asp	Arg	Ile	Asp	Phe	Val	His	Leu	Leu	Leu	Glu	Asn	Gly	Val
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Ser	Met	Gln	Lys	Phe	Leu	Thr	Tyr	Gly	Arg	Leu	Glu	His	Leu	Tyr	Asn
	675						680					685			
Thr	Asp	Lys	Gly	Pro	Gln	Asn	Thr	Leu	Arg	Thr	Asn	Leu	Leu	Val	Asp
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Ser	Lys	His	His	Ile	Lys	Leu	Val	Glu	Val	Gly	Arg	Leu	Val	Glu	Asn
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Leu	Met	Gly	Asn	Leu	Tyr	Lys	Ser	Asn	Tyr	Thr	Lys	Glu	Glu	Phe	Lys
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Asn	Gln	Tyr	Phe	Leu	Phe	Asn	Asn	Arg	Lys	Gln	Phe	Gly	Lys	Arg	Val
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His	Ser	Asn	Ser	Asn	Gly	Gly	Arg	Asn	Asp	Val	Ile	Gly	Pro	Ser	Gly
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980										985					990					
Ala	Ala	Glu	His	Asp	Glu	Glu	Met	Ser	Asp	Ser	Glu	Met	Asn	Ser	Ala					
995										1000					1005					
Glu	Asp	Thr	Asp	Thr	Ser	Ser	Asp	Ser	Ser	Ser	Asp	Ser	Asp	Asp	Ser					
1010										1015					1020					
Asp	Glu	Glu	Asp	Ala	Lys	Leu	Arg	Ala	Gln	Ser	Leu	Ser	Ala	Asp	Gln					
1025	1030										1035					1040				
Pro	Leu	Ser	Ile	His	Arg	Leu	Val	Arg	Asp	Lys	Leu	Asn	Phe	Ser	Glu					
1045										1050					1055					
Lys	Lys	Lys	Pro	Asp	Met	Gly	Ile	Ser	Arg	Ile	Val	Val	Ala	Pro	Pro					
1060										1065					1070					
Ile	Val	Thr	Gly	Arg	Asn	Arg	Ala	Arg	Thr	Met	Ser	Ile	Lys	Lys	Ser					
1075										1080					1085					
Lys	Lys	Asn	Val	Ile	Lys	Pro	Pro	Ala	Cys	Leu	Lys	Ile	Glu	Thr	Ser					
1090										1095					1100					
Asp	Asp	Asp	Glu	Gln	Glu	Gln	Lys	Lys	Ala	Thr	Glu	Met	Cys	Lys	Ser					
1105	1110										1115					1120				
Thr	Phe	Phe	Asp	Phe	Phe	Phe	Asp	Phe	Pro	Tyr	Ile	Asn	Arg	Thr	Gly					
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Lys	Arg	Gly	Ser	Val	Ala	Val	Ala	Met	Asn	His	Asp	Asp	Met	Tyr	Ile					
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Asp	Pro	Ser	Glu	Glu	Leu	Asp	Thr	Gln	Thr	Arg	Gln	Lys	Ser	Ser	Arg					
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Glu	Phe	Ser	Ser	Ser	Arg	Asn	Val	Thr	Val	Gln	Val	Tyr	Thr	Gln	Arg					
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Pro	Leu	Ser	Trp	Lys	Lys	Lys	Ile	Met	Glu	Phe	Tyr	Lys	Ala	Pro	Ile					
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Leu	Thr	Tyr	Asn	Leu	Leu	Val	Lys	Thr	Gln	Arg	Ile	Ala	Ser	Trp	Ser					
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Glu	Trp	Tyr	Val	Phe	Ala	Tyr	Ile	Phe	Val	Trp	Thr	Leu	Glu	Ile	Gly					
1235										1240					1245					

-21-

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Thr	Thr	Lys	Thr	Leu	Gly	Arg	Ile	Leu	Ile	Ile	Cys	Asn	Ser	Val	Ile
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Trp	Ser	Leu	Lys	Leu	Val	Asp	Tyr	Leu	Ser	Val	Gln	Gln	Gly	Leu	Gly
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Pro	Tyr	Ile	Asn	Ile	Val	Ala	Glu	Met	Ile	Pro	Thr	Met	Ile	Pro	Leu
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Cys	Val	Leu	Val	Phe	Ile	Thr	Leu	Tyr	Ala	Phe	Gly	Leu	Leu	Arg	Gln
				1345					1350					1355	
Ser	Ile	Thr	Tyr	Pro	Tyr	Glu	Asp	Trp	His	Trp	Ile	Leu	Val	Arg	Asn
				1365					1370					1375	
Ile	Phe	Leu	Gln	Pro	Tyr	Phe	Met	Leu	Tyr	Gly	Glu	Val	Tyr	Ala	Ala
				1380					1385					1390	
Glu	Ile	Asp	Thr	Cys	Gly	Asp	Glu	Ile	Trp	Gln	Thr	His	Glu	Asp	Glu
				1395					1400					1405	
Asn	Ile	Pro	Ile	Ser	Met	Leu	Asn	Val	Thr	His	Glu	Thr	Cys	Val	Pro
				1410					1415					1420	
Gly	Tyr	Trp	Ile	Ala	Pro	Val	Gly	Leu	Thr	Val	Phe	Met	Leu	Ala	Thr
				1425					1430					1435	
Asn	Val	Leu	Leu	Met	Asn	Val	Met	Val	Ala	Gly	Cys	Thr	Tyr	Ile	Phe
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Glu	Lys	His	Ile	Gln	Ser	Thr	Arg	Glu	Ile	Phe	Leu	Phe	Glu	Arg	Tyr
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Gly	Gln	Val	Met	Glu	Tyr	Glu	Ser	Thr	Pro	Trp	Leu	Pro	Pro	Pro	Phe
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Thr	Ile	Ile	Tyr	His	Val	Ile	Trp	Leu	Phe	Lys	Leu	Ile	Lys	Ser	Ser
				1490					1495					1500	
Ser	Arg	Met	Phe	Glu	Arg	Lys	Asn	Leu	Phe	Asp	Gln	Ser	Leu	Lys	Leu
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Phe	Leu	Ser	Pro	Asp	Glu	Met	Glu	Lys	Val	His	Thr	Phe	Glu	Glu	Glu
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Ser	Val	Glu	Asp	Met	Lys	Arg	Glu	Thr	Glu	Lys	Lys	Asn	Leu	Ser	Ser
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Asn	Asp	Glu	Arg	Ile	His	Arg	Thr	Ala	Glu	Arg	Thr	Asp	Ala	Ile	Leu
				1555					1560					1565	
Asn	Arg	Val	Ser	His	Leu	Thr	Gln	Leu	Glu	Phe	Thr	Leu	Lys	Glu	Glu
				1570					1575					1580	
Ile	Arg	Glu	Leu	Glu	His	Lys	Met	Lys	Asn	Met	Asp	Ser	Arg	His	Lys
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Glu	Gln	Met	Asn	Leu	Met	Leu	Asp	Met	Asn	Lys	Lys	Leu	Gly	Lys	Phe
				1605					1610					1615	
Ile	Ser	Gly	Lys	Tyr	Lys	Arg	Gly	Ser	Phe	Gly	Gly	Ser	Gly	Ser	Asp
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Gly	Gly	Gly	Gly	Ser	Ser	Asp	Asn	Ser	Lys	Leu	Glu	Pro	Asn	Asn	Ser
				1635					1640					1645	
Val	Pro	Met	Ile	Thr	Val	Asp	Gly	Pro	Ser	Pro	Ile	Gly	Ser	Arg	Arg
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Thr	Ser	Gly	Gln	Tyr	Leu	Lys	Arg	Asp	Ser	Leu	Gln	Ala	Lys	Lys	Lys
				1665					1670					1675	
Ile	Thr	Glu	Asn	Arg	Ser	Ser	Leu	Glu	Gln	Pro	Lys	Ile	Pro	Ser	Ser
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Ile	Gln	Phe	Asn	Leu	Met	Glu	Asp	Gln	Asp	Glu	Ser	Ala	Ala	Glu	Ser
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Ala	Thr	Glu	Glu	Val	Ser	Ile	Ser	Ile	Pro	Val	Pro	Gln	Met	Arg	Val
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Arg	Gln	Val	Thr	Glu	Ser	Asp	Lys	Ser	Asp	Leu	Ser	Glu	Asp	Asp	Leu
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Ile	Thr	Arg	Glu	Asp	Ala	Pro	Pro	Thr	Ser	Ile	Asn	Leu	Pro	Arg	Gly
				1745					1750					1755	
Pro	Arg	Arg	His	Ala	Leu	Tyr	Ser	Thr	Ile	Ala	Asp	Ala	Ile	Glu	Thr

-22-

		1765		1770		1775									
Glu	Asp	Asp	Phe	Tyr	Ala	Asp	Ser	Pro	Val	Pro	Met	Pro	Met	Thr	Pro
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Val	Gln	Pro	Ala	Asp	Gly	Ser	Phe	Phe	Gly	Glu	Asn	Asp	Ser	Arg	Tyr
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		20					25						30		
Ala	Pro	Arg	Asn	Ser	Met	Cys	Asn	Ala	Asn	Thr	Val	His	Ser	Ile	Ser
		35				40						45			
Ser	Phe	Arg	Ser	Asp	His	Leu	Ser	Arg	Lys	Ser	Thr	His	Lys	Phe	Leu
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Asp	Asn	Pro	Asn	Leu	Phe	Ala	Ile	Glu	Leu	Thr	Glu	Lys	Leu	Ser	Pro
65				70					75					80	
Pro	Trp	Ile	Glu	Asn	Thr	Phe	Glu	Lys	Arg	Glu	Cys	Ile	Arg	Phe	Ala
			85					90						95	
Ala	Leu	Pro	Lys	Asp	Pro	Glu	Arg	Cys	Gly	Cys	Gly	Arg	Pro	Leu	Ser
			100					105					110		
Ala	His	Thr	Pro	Ala	Ser	Thr	Phe	Phe	Ser	Thr	Leu	Pro	Val	His	Leu
		115					120						125		
Leu	Glu	Lys	Glu	Gln	Gln	Thr	Trp	Thr	Ile	Ala	Asn	Asn	Thr	Gln	Thr
	130					135					140				
Ser	Thr	Thr	Asp	Ala	Phe	Gly	Thr	Ile	Val	Phe	Gln	Gly	Gly	Ala	His
145				150						155					160
Ala	His	Lys	Ala	Gln	Tyr	Val	Arg	Leu	Ser	Tyr	Asp	Ser	Glu	Pro	Leu
			165						170					175	
Asp	Val	Met	Tyr	Leu	Met	Glu	Lys	Val	Trp	Gly	Leu	Glu	Ala	Pro	Arg
		180					185						190		
Leu	Val	Ile	Thr	Val	His	Gly	Gly	Met	Ser	Asn	Phe	Glu	Leu	Glu	Glu
	195					200						205			
Arg	Leu	Gly	Arg	Leu	Phe	Arg	Lys	Gly	Met	Leu	Lys	Ala	Ala	Gln	Thr
	210					215						220			
Thr	Gly	Ala	Trp	Ile	Ile	Thr	Ser	Gly	Leu	Asp	Ser	Gly	Val	Val	Arg
225				230						235					240
His	Val	Ala	Lys	Ala	Leu	Asp	Glu	Ala	Gly	Ile	Ser	Ala	Arg	Met	Arg
			245						250					255	
Ser	Gln	Ile	Val	Thr	Ile	Gly	Ile	Ala	Pro	Trp	Gly	Val	Ile	Lys	Arg
		260						265					270		
Lys	Glu	Arg	Leu	Ile	Arg	Gln	Asn	Glu	His	Val	Tyr	Tyr	Asp	Val	His
	275						280					285			
Ser	Leu	Ser	Val	Asn	Ala	Asn	Val	Gly	Ile	Leu	Asn	Asp	Arg	His	Ser
	290					295					300				
Tyr	Phe	Leu	Leu	Ala	Asp	Asn	Gly	Thr	Val	Gly	Arg	Phe	Gly	Ala	Asp
305				310						315					320
Leu	His	Leu	Arg	Gln	Asn	Leu	Glu	Asn	His	Ile	Ala	Thr	Phe	Gly	Cys
			325						330					335	
Asn	Gly	Arg	Lys	Val	Pro	Val	Val	Cys	Thr	Leu	Leu	Glu	Gly	Gly	Ile
		340						345					350		
Ser	Ser	Ile	Asn	Ala	Ile	His	Asp	Tyr	Val	Thr	Met	Lys	Pro	Asp	Ile
		355					360					365			

-23-

Pro	Ala	Ile	Val	Cys	Asp	Gly	Ser	Gly	Arg	Ala	Ala	Asp	Ile	Ile	Ser
370						375				380					
Phe	Ala	Ala	Arg	Tyr	Ile	Asn	Ser	Asp	Gly	Thr	Phe	Ala	Ala	Glu	Val
385					390					395					400
Gly	Glu	Lys	Leu	Arg	Asn	Leu	Ile	Lys	Met	Val	Phe	Pro	Glu	Thr	Asp
				405					410					415	
Gln	Glu	Glu	Met	Phe	Arg	Lys	Ile	Thr	Glu	Cys	Val	Ile	Arg	Asp	Asp
			420						425				430		
Leu	Leu	Arg	Ile	Phe	Arg	Tyr	Gly	Gln	Glu	Glu	Glu	Glu	Asp	Val	Asp
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Phe	Val	Ile	Leu	Ser	Thr	Val	Leu	Gln	Lys	Gln	Asn	Leu	Pro	Pro	Asp
	450					455					460				
Glu	Gln	Leu	Ala	Leu	Thr	Leu	Ser	Trp	Asn	Arg	Val	Asp	Leu	Ala	Lys
465					470					475					480
Ser	Cys	Leu	Phe	Ser	Asn	Gly	Arg	Lys	Trp	Ser	Ser	Asp	Val	Leu	Glu
				485					490					495	
Lys	Ala	Met	Asn	Asp	Ala	Leu	Tyr	Trp	Asp	Arg	Val	Asp	Phe	Val	Glu
			500					505					510		
Cys	Leu	Leu	Glu	Asn	Gly	Val	Ser	Met	Lys	Asn	Phe	Leu	Ser	Ile	Asn
		515					520					525			
Arg	Leu	Glu	Asn	Leu	Tyr	Asn	Met	Asp	Asp	Ile	Asn	Ser	Ala	His	Ser
	530					535						540			
Val	Arg	Asn	Trp	Met	Glu	Asn	Phe	Asp	Ser	Met	Asp	Pro	His	Thr	Tyr
545					550					555					560
Leu	Thr	Ile	Pro	Met	Ile	Gly	Gln	Val	Val	Glu	Lys	Leu	Met	Gly	Asn
				565					570					575	
Ala	Phe	Gln	Leu	Tyr	Tyr	Thr	Ser	Arg	Ser	Phe	Lys	Gly	Lys	Tyr	Asp
			580					585					590		
Arg	Tyr	Lys	Arg	Ile	Asn	Gln	Ser	Ser	Tyr	Phe	His	Arg	Lys	Arg	Lys
		595					600					605			
Ile	Val	Gln	Lys	Glu	Leu	Phe	Lys	Lys	Lys	Ser	Asp	Asp	Gln	Ile	Asn
	610					615					620				
Asp	Asn	Glu	Glu	Glu	Asp	Phe	Ser	Phe	Ala	Tyr	Pro	Phe	Asn	Asp	Leu
625					630					635					640
Leu	Ile	Trp	Ala	Val	Leu	Thr	Ser	Arg	His	Gly	Met	Ala	Glu	Cys	Met
				645					650					655	
Trp	Val	His	Gly	Glu	Asp	Ala	Met	Ala	Lys	Cys	Leu	Leu	Ala	Ile	Arg
			660					665					670		
Leu	Tyr	Lys	Ala	Thr	Ala	Lys	Ile	Ala	Glu	Asp	Glu	Tyr	Leu	Asp	Val
		675					680					685			
Glu	Glu	Ala	Lys	Arg	Leu	Phe	Asp	Asn	Ala	Val	Lys	Cys	Arg	Glu	Asp
	690					695					700				
Ala	Ile	Glu	Leu	Leu	Asp	Gln	Cys	Tyr	Arg	Ala	Asp	His	Asp	Arg	Thr
705					710					715					720
Leu	Arg	Leu	Leu	Arg	Met	Glu	Leu	Pro	His	Trp	Gly	Asn	Asn	Asn	Cys
				725					730					735	
Leu	Ser	Leu	Ala	Val	Leu	Ala	Asn	Thr	Lys	Thr	Phe	Leu	Ala	His	Pro
		740					745						750		
Cys	Cys	Gln	Ile	Leu	Leu	Ala	Glu	Leu	Trp	His	Gly	Ser	Leu	Lys	Val
		755					760					765			
Arg	Ser	Gly	Ser	Asn	Val	Arg	Val	Leu	Thr	Ala	Leu	Ile	Cys	Pro	Pro
	770					775					780				
Ala	Ile	Leu	Phe	Met	Ala	Tyr	Lys	Pro	Lys	His	Ser	Lys	Thr	Ala	Arg
785					790					795					800
Leu	Leu	Ser	Glu	Glu	Thr	Pro	Glu	Gln	Leu	Pro	Tyr	Pro	Arg	Glu	Ser
			805						810					815	
Ile	Thr	Ser	Thr	Ser	Asn	Arg	Tyr	Arg	Tyr	Ser	Lys	Gly	Pro	Glu	
			820				825					830			
Glu	Gln	Lys	Glu	Thr	Leu	Leu	Glu	Lys	Gly	Ser	Tyr	Thr	Lys	Lys	Val
		835					840					845			

-24-

Thr Ile Ile Ser Ser Arg Lys Asn Ser Gly Val Ala Ser Val Tyr Gly
 850 855 860
 Ser Ala Ser Ser Met Met Phe Lys Arg Glu Pro Gln Leu Asn Lys Phe
 865 870 875 880
 Glu Arg Phe Arg Ala Phe Tyr Ser Ser Pro Ile Thr Lys Phe Trp Ser
 885 890 895
 Trp Cys Ile Ala Phe Leu Ile Phe Leu Thr Thr Gln Thr Cys Ile Leu
 900 905 910
 Leu Leu Glu Thr Ser Leu Lys Pro Ser Lys Tyr Glu Trp Ile Thr Phe
 915 920 925
 Ile Tyr Thr Val Thr Leu Ser Val Glu His Ile Arg Lys Leu Met Thr
 930 935 940
 Ser Glu Gly Ser Arg Ile Asn Glu Lys Val Lys Val Phe Tyr Ala Lys
 945 950 955 960
 Trp Tyr Asn Ile Trp Thr Ser Ala Ala Leu Leu Phe Phe Leu Val Gly
 965 970 975
 Tyr Gly Phe Arg Leu Val Pro Met Tyr Arg His Ser Trp Gly Arg Val
 980 985 990
 Leu Leu Ser Phe Ser Asn Val Leu Phe Tyr Met Lys Ile Phe Glu Tyr
 995 1000 1005
 Leu Ser Val His Pro Leu Leu Gly Pro Tyr Ile Gln Met Ala Ala Lys
 1010 1015 1020
 Met Val Trp Ser Met Cys Tyr Ile Cys Val Leu Leu Leu Val Pro Leu
 1025 1030 1035 104
 Met Ala Phe Gly Val Asn Arg Gln Ala Leu Thr Glu Pro Asn Val Lys
 1045 1050 1055
 Asp Trp His Trp Leu Leu Val Arg Asn Ile Phe Tyr Lys Pro Tyr Phe
 1060 1065 1070
 Met Leu Tyr Gly Glu Val Tyr Ala Gly Glu Ile Asp Thr Cys Gly Asp
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 Glu Gly Ile Arg Cys Phe Pro Gly Tyr Phe Ile Pro Pro Leu Leu Met
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 Val Ile Phe Leu Leu Val Ala Asn Ile Leu Leu Leu Asn Leu Leu Ile
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 Ala Ile Phe Asn Asn Ile Tyr Asn Asp Ser Ile Glu Lys Ser Lys Glu
 1125 1130 1135
 Ile Trp Leu Phe Gln Arg Tyr Gln Gln Leu Met Glu Tyr His Asp Ser
 1140 1145 1150
 Pro Phe Leu Pro Pro Phe Ser Ile Phe Ala His Val Tyr His Phe
 1155 1160 1165
 Ile Asp Tyr Leu Tyr Asn Leu Arg Arg Pro Asp Thr Lys Arg Phe Arg
 1170 1175 1180
 Ser Glu His Ser Ile Lys Leu Ser Val Thr Glu Asp Glu Met Lys Arg
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 Ile Gln Asp Phe Glu Glu Asp Cys Ile Asp Thr Leu Thr Arg Ile Arg
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 Lys Leu Lys Leu Asn Thr Lys Glu Pro Leu Ser Val Thr Asp Leu Thr
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 Glu Leu Thr Cys Gln Arg Val His Asp Leu Met Gln Glu Asn Phe Leu
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 Leu Lys Ser Arg Val Tyr Asp Ile Glu Thr Lys Ile Asp His Ile Ser
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 Asn Ser Ser Asp Glu Val Val Gln Ile Leu Lys Asn Lys Lys Leu Ser
 1265 1270 1275 128
 Gln Asn Phe Ala Ala Ser Ser Leu Ser Leu Pro Asp Thr Ser Ile Glu
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 Val Pro Lys Ile Thr Lys Thr Leu Ile Asp Cys His Leu Ser Pro Val
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 Ser Ile Glu Asp Arg Leu Ala Thr Arg Ser Pro Leu Leu Ala Asn Leu
 1315 1320 1325

-25-

Gln Arg Asp His Thr Leu Arg Lys Leu Pro Thr Trp Glu Thr Ser Thr
 1330 1335 1340
 Ala Ser Thr Ser Ser Phe Glu Phe Val Phe Tyr Phe Thr Arg His Glu
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 Gly Asn Glu Asn Lys Tyr Glu Phe Lys Lys Leu Glu Lys Gly Gly Phe
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 35 40 45
 Ala Gly Gly Asp Gly Asn Ala Val Pro Thr Thr Ser Gln Ala Gln Ala
 50 55 60
 Gln Thr Phe Asn Ser Gly Arg Gln Thr Thr Gly Met Ser Ser Gly Asp
 65 70 75 80
 Arg Leu Asn Glu Asp Val Ser Ala Thr Ala Asn Ser Ala Gln Leu Val
 85 90 95
 Leu Pro Thr Pro Leu Phe Asn Gln Met Arg Phe Thr Glu Ser Asn Met
 100 105 110
 Ser Leu Asn Arg His Asn Trp Val Arg Glu Thr Phe Thr Arg Arg Glu
 115 120 125
 Cys Ser Arg Phe Ile Ala Ser Ser Arg Asp Leu His Lys Cys Gly Cys
 130 135 140
 Gly Arg Thr Arg Asp Ala His Arg Asn Ile Pro Glu Leu Thr Ser Glu
 145 150 155 160
 Phe Leu Arg Gln Lys Arg Ser Val Ala Ala Leu Glu Gln Gln Arg Ser
 165 170 175
 Ile Ser Asn Val Asn Asp Asp Ile Asn Thr Gln Asn Met Tyr Thr Lys
 180 185 190
 Arg Gly Ala Asn Glu Lys Trp Ser Leu Arg Lys His Thr Val Ser Leu
 195 200 205
 Ala Thr Asn Ala Phe Gly Gln Val Glu Phe Gln Gly Gly Pro His Pro
 210 215 220
 Tyr Lys Ala Gln Tyr Val Arg Val Asn Phe Asp Thr Glu Pro Ala Tyr
 225 230 235 240
 Ile Met Ser Leu Phe Glu His Val Trp Gln Ile Ser Pro Pro Arg Leu
 245 250 255
 Ile Ile Thr Val His Gly Gly Thr Ser Asn Phe Asp Leu Gln Pro Lys
 260 265 270
 Leu Ala Arg Val Phe Arg Lys Gly Leu Leu Lys Ala Ala Ser Thr Thr
 275 280 285
 Gly Ala Trp Ile Ile Thr Ser Gly Cys Asp Thr Gly Val Val Lys His
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 Val Ala Ala Ala Leu Glu Gly Ala Gln Ser Ala Gln Arg Asn Lys Ile
 305 310 315 320
 Val Cys Ile Gly Ile Ala Pro Trp Gly Leu Leu Lys Lys Arg Glu Asp
 325 330 335
 Phe Ile Gly Gln Asp Lys Thr Val Pro Tyr Tyr Pro Ser Ser Ser Lys
 340 345 350
 Gly Arg Phe Thr Gly Leu Asn Asn Arg His Ser Tyr Phe Leu Leu Val

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Asp	Asn	Gly	Thr	Val	Gly	Arg	Tyr	Gly	Ala	Glu	Val	Ile	Leu	Arg	Lys
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Arg	Leu	Glu	Met	Tyr	Ile	Ser	Gln	Lys	Gln	Lys	Ile	Phe	Gly	Gly	Thr
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Arg	Ser	Val	Pro	Val	Val	Cys	Val	Val	Leu	Glu	Gly	Gly	Ser	Cys	Thr
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Ile	Arg	Ser	Val	Leu	Asp	Tyr	Val	Thr	Asn	Val	Pro	Arg	Val	Pro	Val
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Val	Val	Cys	Asp	Gly	Ser	Gly	Arg	Ala	Ala	Asp	Leu	Leu	Ala	Phe	Ala
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His	Gln	Asn	Val	Thr	Glu	Asp	Gly	Leu	Leu	Pro	Asp	Asp	Ile	Arg	Arg
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Gln	Val	Leu	Leu	Leu	Val	Glu	Thr	Thr	Phe	Gly	Cys	Ser	Glu	Ala	Ala
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Ala	His	Arg	Leu	Leu	His	Glu	Leu	Thr	Val	Cys	Ala	Gln	His	Lys	Asn
			485					490					495		
Leu	Leu	Thr	Ile	Phe	Arg	Leu	Gly	Glu	Gln	Gly	Glu	His	Asp	Val	Asp
		500					505						510		
His	Ala	Ile	Leu	Thr	Ala	Leu	Leu	Lys	Gly	Gln	Asn	Leu	Ser	Ala	Ala
		515				520						525			
Asp	Gln	Leu	Ala	Leu	Ala	Leu	Ala	Trp	Asn	Arg	Val	Asp	Ile	Ala	Arg
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Ser	Asp	Val	Phe	Ala	Met	Gly	His	Glu	Trp	Pro	Gln	Ala	Ala	Leu	His
545				550						555					560
Asn	Ala	Met	Met	Glu	Ala	Leu	Ile	His	Asp	Arg	Val	Asp	Phe	Val	Arg
			565					570						575	
Leu	Leu	Leu	Glu	Gln	Gly	Ile	Asn	Met	Gln	Lys	Phe	Leu	Thr	Ile	Ser
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Arg	Leu	Asp	Glu	Leu	Tyr	Asn	Thr	Asp	Lys	Gly	Pro	Pro	Asn	Thr	Leu
		595				600						605			
Phe	Tyr	Ile	Val	Arg	Asp	Val	Val	Arg	Val	Arg	Gln	Gly	Tyr	Arg	Phe
610					615					620					
Lys	Leu	Pro	Asp	Ile	Gly	Leu	Val	Ile	Glu	Lys	Leu	Met	Gly	Asn	Ser
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Tyr	Gln	Cys	Ser	Tyr	Thr	Thr	Ser	Glu	Phe	Arg	Asp	Lys	Tyr	Lys	Gln
			645					650						655	
Arg	Met	Lys	Arg	Val	Lys	His	Ala	Gln	Lys	Lys	Ala	Met	Gly	Val	Phe
			660				665						670		
Ser	Ser	Arg	Pro	Ser	Arg	Thr	Gly	Ser	Gly	Ile	Ala	Ser	Arg	Gln	Ser
		675				680						685			
Thr	Glu	Gly	Met	Gly	Gly	Val	Gly	Gly	Gly	Ser	Ser	Val	Ala	Gly	Val
690				695						700					
Phe	Gly	Asn	Ser	Phe	Gly	Asn	Gln	Asp	Pro	Pro	Leu	Asp	Pro	His	Val
705				710					715					720	
Asn	Arg	Ser	Ala	Leu	Ser	Gly	Ser	Arg	Ala	Leu	Ser	Asn	His	Ile	Leu
			725					730						735	
Trp	Arg	Ser	Ala	Phe	Arg	Gly	Asn	Phe	Pro	Ala	Asn	Pro	Met	Arg	Pro
			740				745						750		
Pro	Asn	Leu	Gly	Asp	Ser	Arg	Asp	Cys	Gly	Ser	Glu	Phe	Asp	Glu	Glu
		755				760						765			
Leu	Ser	Leu	Thr	Ser	Ala	Ser	Asp	Gly	Ser	Gln	Thr	Glu	Pro	Asp	Phe
770				775								780			
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785				790					795					800	
Gln	Asp	Met	Ala	Met	Cys	Met	Trp	Gln	His	Gly	Glu	Glu	Ala	Met	Ala
			805					810						815	
Lys	Ala	Leu	Val	Ala	Cys	Arg	Leu	Tyr	Lys	Ser	Leu	Ala	Thr	Glu	Ala
			820				825						830		
Ala	Glu	Asp	Tyr	Leu	Glu	Val	Glu	Ile	Cys	Glu	Glu	Leu	Lys	Lys	Tyr

-27-

835	840	845
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850	855	860
His Val Asp Asp Ala Gln Thr Leu Gln Leu Leu Thr Tyr Glu Leu Ser		
865	870	875
Asn Trp Ser Asn Glu Thr Cys Leu Ala Leu Ala Val Ile Val Asn Asn		
885	890	895
Lys His Phe Leu Ala His Pro Cys Cys Gln Ile Leu Leu Ala Asp Leu		
900	905	910
Trp His Gly Gly Leu Arg Met Arg Thr His Ser Asn Ile Lys Val Val		
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Leu Gly Leu Ile Cys Pro Pro Phe Ile Gln Met Leu Glu Phe Lys Thr		
930	935	940
Arg Glu Glu Leu Leu Asn Gln Pro Gln Thr Ala Ala Glu His Gln Asn		
945	950	955
Asp Met Asn Tyr Ser Ser Ser Ser Ser Ser Ser Ser Ser Ser Ser		
965	970	975
Ser Ser Ser Ser Ser Asp Ser Ser Ser Phe Glu Asp Asp Asp Asp Glu		
980	985	990
Asn Asn Ala His Asn His Asp Gln Lys Arg Thr Arg Lys Thr Ser Gln		
995	1000	1005
Gly Ser Ala Gln Ser Leu Asn Ile Thr Ser Leu Phe His Ser Arg Arg		
1010	1015	1020
Arg Lys Ala Lys Lys Asn Glu Lys Cys Asp Arg Glu Thr Asp Ala Ser		
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Ala Cys Glu Ala Gly Asn Arg Gln Ile Gln Asn Gly Gly Leu Thr Ala		
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Glu Tyr Gly Thr Phe Gly Glu Ser Asn Gly Val Ser Pro Pro Pro Pro		
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Tyr Met Arg Ala Asn Ser Arg Ser Arg Tyr Asn Asn Arg Ser Asp Met		
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Ser Lys Thr Ser Ser Val Ile Phe Gly Ser Asp Pro Asn Leu Ser Lys		
1090	1095	1100
Leu Gln Lys Ser Asn Ile Thr Ser Thr Asp Arg Pro Asn Pro Met Glu		
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Gln Phe Gln Gly Thr Arg Lys Ile Lys Met Arg Arg Arg Phe Tyr Glu		
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Phe Tyr Ser Ala Pro Ile Ser Thr Phe Trp Ser Trp Thr Ile Ser Phe		
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Ile Leu Phe Ile Thr Phe Phe Thr Tyr Thr Leu Leu Val Lys Thr Pro		
1155	1160	1165
Pro Arg Pro Thr Val Ile Glu Tyr Ile Leu Ile Ala Tyr Val Ala Ala		
1170	1175	1180
Phe Gly Leu Glu Gln Val Arg Lys Ile Ile Met Ser Asp Ala Lys Pro		
1185	1190	1195
Phe Tyr Glu Lys Ile Arg Thr Tyr Val Cys Ser Phe Trp Asn Cys Val		
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Thr Ile Leu Ala Ile Ile Phe Tyr Ile Val Gly Phe Phe Met Arg Cys		
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Phe Gly Ser Val Ala Tyr Gly Arg Val Ile Leu Ala Cys Asp Ser Val		
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Leu Trp Thr Met Lys Leu Leu Asp Tyr Met Ser Val His Pro Lys Leu		
1250	1255	1260
Gly Pro Tyr Val Thr Met Ala Gly Lys Met Ile Gln Asn Met Ser Tyr		
1265	1270	1275
Ile Ile Val Met Leu Val Val Thr Leu Leu Ser Phe Gly Leu Ala Arg		
1285	1290	1295
Gln Ser Ile Thr Tyr Pro Asp Glu Thr Trp His Trp Ile Leu Val Arg		
1300	1305	1310
Asn Ile Phe Leu Lys Pro Tyr Phe Met Leu Tyr Gly Glu Val Tyr Ala		

-28-

1315	1320	1325
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Asn Gly Gly Pro Val Ile Leu Gly Asn Gly Thr Thr Gly Leu Ser Cys		
1345	1350	1355
Val Pro Gly Tyr Trp Ile Pro Pro Leu Leu Met Thr Phe Phe Leu Leu		
1365	1370	1375
Ile Ala Asn Ile Leu Leu Met Ser Met Leu Ile Ala Ile Phe Asn His		
1380	1385	1390
Ile Phe Asp Ala Thr Asp Glu Met Ser Gln Gln Ile Trp Leu Phe Gln		
1395	1400	1405
Arg Tyr Lys Gln Val Met Glu Tyr Glu Ser Thr Pro Phe Leu Pro Pro		
1410	1415	1420
Pro Leu Thr Pro Leu Tyr His Gly Val Leu Ile Leu Gln Phe Val Arg		
1425	1430	1435
Thr Arg Leu Ser Cys Ser Lys Ser Gln Glu Arg Asn Pro Ile Leu Leu		
1445	1450	1455
Leu Lys Ile Ala Glu Leu Phe Leu Asp Asn Asp Gln Ile Glu Lys Leu		
1460	1465	1470
His Asp Phe Glu Glu Asp Cys Met Glu Asp Leu Ala Arg Gln Lys Leu		
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Asn Glu Lys Asn Thr Ser Asn Glu Gln Arg Ile Leu Arg Ala Asp Ile		
1490	1495	1500
Arg Thr Asp Gln Ile Leu Asn Arg Leu Ile Asp Leu Gln Ala Lys Glu		
1505	1510	1515
Ser Met Gly Arg Asp Val Ile Asn Asp Val Glu Ser Arg Leu Ala Ser		
1525	1530	1535
Val Glu Lys Ala Gln Asn Glu Ile Leu Glu Cys Val Arg Ala Leu Leu		
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Asn Gln Asn Asn Ala Pro Thr Ala Ile Gly Arg Cys Phe Ser Pro Ser		
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Pro Asp Pro Leu Val Glu Thr Ala Asn Gly Thr Pro Gly Pro Leu Leu		
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Leu Lys Leu Pro Gly Thr Asp Pro Ile Leu Glu Glu Lys Asp His Asp		
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Ser Gly Glu Asn Ser Asn Ser Leu Pro Pro Gly Arg Ile Arg Arg Asn		
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Arg Thr Ala Thr Ile Cys Gly Gly Tyr Val Ser Glu Glu Arg Asn Met		
1620	1625	1630
Met Leu Leu Ser Pro Lys Pro Ser Asp Val Ser Gly Ile Pro Gln Gln		
1635	1640	1645
Arg Leu Met Ser Val Thr Ser Met Asp Pro Leu Pro Leu Pro Leu Ala		
1650	1655	1660
Lys Leu Ser Thr Met Ser Ile Arg Arg Arg His Glu Glu Tyr Thr Ser		
1665	1670	1675
Ile Thr Asp Ser Ile Ala Ile Arg His Pro Glu Arg Arg Ile Arg Asn		
1685	1690	1695
Asn Arg Ser Asn Ser Ser Glu His Asp Glu Ser Ala Val Asp Ser Glu		
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Gly Gly Gly Asn Val Thr Ser Ser Pro Arg Lys Arg Ser Thr Arg Asp		
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Leu Arg Met Thr Pro Ser Ser Gln Val Glu Glu Ser Thr Ser Arg Asp		
1730	1735	1740
Gln Ile Phe Glu Ile Asp His Pro Glu His Glu Glu Asp Glu Ala Gln		
1745	1750	1755
Ala Asp Cys Glu Leu Thr Asp Val Ile Thr Glu Glu Glu Asp Glu Glu		
1765	1770	1775
Glu Asp Asp Glu Glu Asp Asp Ser His Glu Arg His His Ile His Pro		
1780	1785	1790
Arg Arg Lys Ser Ser Arg Gln Asn Arg Gln Pro Ser His Thr Leu Glu		

-29-

1795	1800	1805
Thr Asp Leu Ser Glu Gly Glu Glu Val Asp Pro Leu Asp Val Leu Lys		
1810	1815	1820
Met Lys Glu Leu Pro Ile Ile His Gln Ile Leu Asn Glu Glu Glu Gln		
1825	1830	1835
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Arg Ala Asp Leu Thr Ser Gln Lys Cys Ser Asp Val		1855
1860	1865	

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 <211> 489
 <212> DNA
 <213> Mus Musculus

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<210> 17
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 <212> PRT
 <213> Mus Musculus

<400> 17

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Lys Gln His Ala Cys Phe Thr Ala Ser Leu Ala Met Lys Tyr Ser Asp	
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Val Lys Leu Gly Glu His Phe Asn Gln Ala Ile Glu Glu Trp Ser Val	
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-30-

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caactggggc	gcactgtcct	ctgcatcgac	ttcatgggtt	tcacgggtgc	gctgcttcac	240
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gacgtgttct	tcttcctctt	cttcctcggc	gtgtggctgg	tagctatggg	ttggggccacg	360
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<211> 131

<212> PRT

<213> Homo Sapiens

<220>

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<221> UNSURE

<222> (131)...(131)

<223> UNKNOWN

<400> 19

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			20					25					30		
Gln	Cys	Asp	Leu	Val	Ala	Leu	Thr	Cys	Phe	Leu	Leu	Gly	Val	Gly	Cys
		35					40					45			
Arg	Leu	Thr	Pro	Gly	Leu	Tyr	His	Leu	Gly	Arg	Thr	Val	Leu	Cys	Ile
		50				55					60				
Asp	Phe	Met	Val	Phe	Thr	Val	Arg	Leu	Leu	His	Ile	Phe	Thr	Val	Asn
65					70					75					80
Lys	Gln	Leu	Gly	Pro	Lys	Ile	Val	Ile	Val	Ser	Lys	Met	Met	Lys	Asp
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Val	Phe	Phe	Phe	Leu	Phe	Phe	Leu	Gly	Val	Trp	Leu	Val	Ala	Met	Gly
			100					105					110		
Trp	Ala	Thr	Glu	Gly	Phe	Leu	Arg	Pro	Arg	Asp	Ser	Asp	Phe	Pro	Ser
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Ile	Leu	Xaa													
130															

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<211> 389

<212> DNA

<213> Homo Sapiens

<400> 20

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-31-

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<210> 21

<211> 415

<212> DNA

<213> Homo Sapiens

<400> 21

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<210> 22

<211> 405

<212> DNA

<213> Mus Musculus

<400> 22

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<210> 23

<211> 5117

<212> DNA

<213> Homo Sapiens

<220>

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-33-

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 Ala Val Glu Leu Leu Glu Gln Ser Phe Arg Gln Asp Glu Thr Met Ala
 50 55 60
 Met Lys Leu Leu Thr Tyr Glu Leu Lys Asn Trp Ser Asn Ser Thr Cys
 65 70 75 80
 Leu Lys Leu Ala Val Ser Ser Arg Leu Arg Pro Phe Val Ala His Thr
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Cys	Thr	Gln	Met 100	Leu	Leu	Ser	Asp	Met 105	Trp	Met	Gly	Arg	Leu 110	Asn	Met
Arg	Lys	Asn 115	Ser	Trp	Tyr	Lys	Val 120	Ile	Leu	Ser	Ile	Leu 125	Val	Pro	Pro
Ala	Ile	Leu 130	Leu	Leu	Glu	Tyr 135	Lys	Thr	Lys	Ala	Glu	Met 140	Ser	His	Ile
Pro 145	Gln	Ser	Gln	Asp	Ala 150	His	Gln	Met	Thr	Met 155	Asp	Asp	Ser	Glu	Asn 160
Asn	Phe	Gln	Asn 165	Ile	Thr	Glu	Glu	Ile	Pro	Met 170	Glu	Val	Phe	Lys	Glu
Val	Arg	Ile 180	Leu	Asp	Ser	Asn	Glu	Gly 185	Lys	Asn	Glu	Met 190	Glu	Ile	Gln
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Pro	Ser	Val	Gln 245	Glu	Trp	Ile	Val	Ile	Ala	Tyr 250	Ile	Phe	Thr	Tyr	Ala 255
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Gln	Lys	Ile 275	Lys	Val	Trp	Phe 280	Ser	Asp	Tyr	Phe	Asn	Ile 285	Ser	Asp	Thr
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Lys 305	Trp	Asn	Phe	Ala	Asn 310	Ala	Tyr	Asp	Asn	His 315	Val	Phe	Val	Ala	Gly 320
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Thr	Ser	Asp 515	Gly	Pro	Lys	Leu	Phe 520	Leu	Thr	Glu	Glu	Asp 525	Gln	Lys	Lys
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Glu	Arg	Val	Glu 565	Gln	Met	Cys	Ile	Gln	Ile	Lys 570	Glu	Val	Gly	Asp	Arg

-35-

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His	Leu	Gln	Asp	Leu	Ser	Ala	Leu	Thr	Val	Asp	Thr	Leu	Lys	Thr	Leu
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Gly	Pro	Val	Arg	Pro	Ser	Val	Trp	Lys	Lys	His	Gly	Val	Val	Asn	Thr
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Pro	Glu	Ala	Gly	Ser	Ser	Ser	Gly	Ala	Leu	Phe	Pro	Ser	Ala	Val	Ser
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Pro	Pro	Glu	Leu	Arg	Gln	Arg	Leu	His	Gly	Val	Glu	Leu	Leu	Lys	Ile
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Phe	Asn	Lys	Asn	Gln	Lys	Leu	Gly	Ser	Ser	Ser	Thr	Ser	Ile	Pro	His
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Leu	Ser	Ser	Pro	Pro	Thr	Lys	Phe	Phe	Val	Ser	Thr	Pro	Ser	Gln	Pro
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Gly	His	Arg	Asp	Ser	Met	Asp	Leu	Gln	Arg	Phe	Lys	Glu	Thr	Ser	Asn
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Gln	Lys	Leu	Thr	Phe	Ala	Phe	Asn	Gln	Met	Lys	Pro	Lys	Ser	Ile	Pro
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-36-

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 1075 1080 1085
 Tyr Asn Asn Asn Asn Gly Asp Glu Ile Ile Pro Thr Asn Thr Leu Glu
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 Glu Ile Met Leu Ala Phe Ser His Trp Thr Tyr Glu Tyr Thr Arg Gly
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 Glu Leu Leu Val Leu Asp Leu Gln Gly Val Gly Glu Asn Leu Thr Asp
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 His His Cys Asn Ser Cys Cys Arg Lys Leu Lys Leu Pro Asp Leu Lys
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 Arg Asn Asp Tyr Thr Pro Asp Lys Ile Ile Phe Pro Gln Asp Glu Pro
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<212> DNA

<213> Homo Sapiens

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-37-

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Tyr Phe Trp Glu Met Gly Ser Asn Ala Val Ser Ser Ala Leu Gly Ala
35      40      45
Cys Leu Leu Leu Arg Val Met Ala Arg Leu Glu Pro Asp Ala Glu Glu
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Ala Ala Arg Arg Lys Asp Leu Ala Phe Lys Phe Glu Gly Met Gly Val
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Asp Leu Phe Gly Glu Cys Tyr Arg Ser Ser Glu Val Arg Ala Ala Arg
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Gln Ser Leu Leu Thr Gln Lys Trp Trp Gly Asp Met Ala Ser Thr Thr
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Pro Ile Trp Ala Leu Val Leu Ala Phe Phe Cys Pro Pro Leu Ile Tyr
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Glu Leu Glu Phe Asp Met Asp Ser Val Ile Asn Gly Glu Gly Pro Val
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Gly Thr Ala Asp Pro Ala Glu Lys Thr Pro Leu Gly Val Pro Arg Gln
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Ser Gly Arg Pro Gly Cys Cys Gly Gly Arg Cys Gly Gly Arg Arg Cys
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-38-

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 Asn Lys Gln Leu Gly Pro Lys Ile Val Ile Val Ser Lys Met Met Lys
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 Cys Ser Ser Glu Pro Gly Phe Trp Ala His Pro Pro Gly Ala Gln Ala
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 Gly Thr Cys Val Ser Gln Tyr Ala Asn Trp Leu Val Val Leu Leu Leu
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 Ala Trp Ile Pro Gly Arg Tyr Pro Ser Gly Gly Cys Arg Val Leu Gly
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<212> DNA

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-41-

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 <211> 1865
 <212> PRT
 <213> Homo Sapiens

<400> 28

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Cys	Gln	Ile	Cys	Gln	Gln	Leu	Val	Arg	Cys	Phe	Cys	Gly	Arg	Leu	Val
		35				40						45			
Lys	Gln	His	Ala	Cys	Phe	Thr	Ala	Ser	Leu	Ala	Met	Lys	Tyr	Ser	Asp
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Val	Lys	Leu	Gly	Asp	His	Phe	Asn	Gln	Ala	Ile	Glu	Glu	Trp	Ser	Val
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Glu	Lys	His	Thr	Glu	Gln	Ser	Pro	Thr	Asp	Ala	Tyr	Gly	Val	Ile	Asn
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Phe	Gln	Gly	Gly	Ser	His	Ser	Tyr	Arg	Ala	Lys	Tyr	Val	Arg	Leu	Ser
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Tyr	Asp	Thr	Lys	Pro	Glu	Val	Ile	Leu	Gln	Leu	Leu	Leu	Lys	Glu	Trp
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Gln	Met	Glu	Leu	Pro	Lys	Leu	Val	Ile	Ser	Val	His	Gly	Gly	Met	Gln
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Lys	Phe	Glu	Leu	His	Pro	Arg	Ile	Lys	Gln	Leu	Leu	Gly	Lys	Gly	Leu
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Ile	Lys	Ala	Ala	Val	Thr	Thr	Gly	Ala	Trp	Ile	Leu	Thr	Gly	Gly	Val
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Asn	Thr	Gly	Val	Ala	Lys	His	Val	Gly	Asp	Ala	Leu	Lys	Glu	His	Ala
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Ser	Arg	Ser	Ser	Arg	Lys	Ile	Cys	Thr	Ile	Gly	Ile	Ala	Pro	Trp	Gly
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Val	Ile	Glu	Asn	Arg	Asn	Asp	Leu	Val	Gly	Arg	Asp	Val	Val	Ala	Pro
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Leu	His	Ser	His	Phe	Ile	Leu	Val	Asp	Asp	Gly	Thr	Val	Gly	Lys	Tyr
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Gly	Ala	Glu	Val	Arg	Leu	Arg	Arg	Glu	Leu	Glu	Lys	Thr	Ile	Asn	Gln
		260						265					270		
Gln	Arg	Ile	His	Ala	Arg	Ile	Gly	Gln	Gly	Val	Pro	Val	Val	Ala	Leu
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Ile	Phe	Glu	Gly	Gly	Pro	Asn	Val	Ile	Leu	Thr	Val	Leu	Glu	Tyr	Leu
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Gln	Glu	Ser	Pro	Pro	Val	Pro	Val	Val	Val	Cys	Glu	Gly	Thr	Gly	Arg
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Ala	Ala	Asp	Leu	Leu	Ala	Tyr	Ile	His	Lys	Gln	Thr	Glu	Glu	Gly	Gly
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-42-

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 Ser Asp Glu His Gln Asp Ile Asp Val Ala Ile Leu Thr Ala Leu Leu
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 Lys Gly Thr Asn Ala Ser Ala Phe Asp Gln Leu Ile Leu Thr Leu Ala
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 Trp Asp Arg Val Asp Ile Ala Lys Asn His Val Phe Val Tyr Gly Gln
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 Lys Gln Gly Pro Thr Asn Pro Met Leu Phe His Leu Val Arg Asp Val
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 Thr Cys Thr Gln Met Leu Leu Ser Asp Met Trp Met Gly Arg Leu Asn
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 Pro Ala Ile Leu Leu Leu Glu Tyr Lys Thr Lys Ala Glu Met Ser His
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 Ile Pro Gln Ser Gln Asp Ala His Gln Met Thr Met Asp Asp Ser Glu
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 Asn Asn Phe Gln Asn Ile Thr Glu Glu Ile Pro Met Glu Val Phe Lys
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 Glu Val Arg Ile Leu Asp Ser Asn Glu Gly Lys Asn Glu Met Glu Ile
 820 825 830
 Gln Met Lys Ser Lys Lys Leu Pro Ile Thr Arg Lys Phe Tyr Ala Phe
 835 840 845

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Leu	Pro	Ser	Val	Gln	Glu	Trp	Ile	Val	Ile	Ala	Tyr	Ile	Phe	Thr	Tyr
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Leu	Asp	Phe	Leu	Ala	Val	Asn	Gln	Gln	Ala	Gly	Pro	Tyr	Val	Met	Met
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Ala	Tyr	His	Glu	Lys	Pro	Val	Leu	Pro	Pro	Pro	Leu	Ile	Ile	Leu	Ser
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His	Ile	Val	Ser	Leu	Phe	Cys	Cys	Ile	Cys	Lys	Arg	Arg	Lys	Lys	Asp
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-44-

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 1490 1495 1500
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-45-

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-48-

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<400> 32

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35          40          45
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50          55          60
Glu Asn Val Cys Lys Cys Gly Tyr Ala Gln Ser Gln His Met Glu Gly
65          70          75          80
Thr Gln Ile Asn Gln Ser Glu Lys Trp Asn Tyr Lys Lys His Thr Lys
85          90          95
Glu Phe Pro Thr Asp Ala Phe Gly Asp Ile Gln Phe Glu Thr Leu Gly
100         105         110
Lys Lys Gly Lys Tyr Ile Arg Leu Ser Cys Asp Thr Asp Ala Glu Ile
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-51-

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Lys	Asn	Lys	Ile	Pro	Cys	Val	Val	Val	Glu	Gly	Ser	Gly	Gln	Ile	Ala
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Gly	Val	Gln	Asn	Phe	Leu	Ser	Lys	Gln	Trp	Tyr	Gly	Glu	Ile	Ser	Arg
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-52-

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/29996

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/705 C12N15/12 C12Q1/68 C12N5/10 C07K16/28
G01N33/53 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K C12Q A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, WPI Data, PAJ, MEDLINE, SCISEARCH, EMBASE, BIOTECHNOLOGY
ABS, CHEM ABS Data, STRAND, GENSEQ, EMBL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE GENEMBL 'Online! 16 February 1998 (1998-02-16) STRAUSBERG, R.: "ob70f05.s1 NCI_CGAP_GCB1 Homo sapiens cDNA clone IMAGE:1336737 3', mRNA sequence" XP002138823 Accession AA809355	1,2, 6-19, 25-35
X	DATABASE GENEMBL 'Online! 10 July 1998 (1998-07-10) MARRA ET AL.: "ub28d10.r1 Soares 2NbMT Mus musculus cDNA clone IMAGE:1379059 5' mRNA sequence" XP002149803 Accession AI050262	1,6-19, 25-35
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

16 October 2000

Date of mailing of the international search report

30. 10. 00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Fax: (+31-70) 340-3016

Authorized officer

ALCONADA RODRIG., A

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/29996

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE GENEMBL 'Online! 19 July 1997 (1997-07-19) STRAUSBERG, R.: "ni64e11.s1 NCI_CGAP_Pr12 Homo sapiens cDNA clone IMAGE:981644 mRNA sequence" XP002148641 Accession AA523749	1,3, 10-19, 25-35
X	WO 98 15657 A (ABBOTT LAB) 16 April 1998 (1998-04-16) page 4, line 7 -page 5, line 13 page 5, line 24 -page 7, line 28	1,4, 6-19, 25-35
Y	SEQ ID NOs. 9 and 25	20-24
X	WO 98 37093 A (CORIXA CORP) 27 August 1998 (1998-08-27) page 7, paragraph 2 page 9, paragraphs 2,3 page 13 -page 17 page 21, paragraph 3	1,4, 6-19, 25-35
Y	SEQ ID NOs: 109 and 112	20-24
X	DATABASE GENEMBL 'Online! 18 November 1997 (1997-11-18) STRAUSBERG, R.: "nt76b07.s1 NCI_CGAP_Pr3 Homo sapiens cDNA clone IMAGE:1204405, mRNA" XP002148642	1,5-19, 25-35
Y	Accession AA654650	20-24
Y	DATABASE GENEMBL 'Online! 30 November 1998 (1998-11-30) SHIMIZU, N.: "Homo sapiens mRNA complete cds." XP002148643 Accession number AB001535 -& NAGAMINE ET AL.: "Molecular cloning of a novel putative Ca2+ channel protein (TRPC7) highly expressed in brain" GENOMICS, vol. 54, 15 November 1998 (1998-11-15), pages 124-131, XP000938744 the whole document	20-24

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/29996

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZHU, XI ET AL: "Molecular cloning of a widely expressed human homologue for the <i>Drosophila</i> trp gene." FEBS LETTERS, (1995) VOL. 373, NO. 3, PP. 193-198., XP000907241 page 194; figures 1,3 ---	20,21, 23,25, 26,28, 29,31
A	HUNTER JOHN J ET AL: "Chromosomal localization and genomic characterization of the mouse melastatin gene (<i>Mln1</i>)." GENOMICS NOV. 15, 1998, vol. 54, no. 1, 15 November 1998 (1998-11-15), pages 116-123, XP000910696 ISSN: 0888-7543 cited in the application page 119; figure 2 ---	20,21,23
A	WES PAUL D ET AL: "TRPC1, a human homolog of a <i>Drosophila</i> store-operated channel." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 1995, vol. 92, no. 21, 1995, pages 9652-9656, XP002138820 ISSN: 0027-8424 the whole document ---	20,21, 23,25, 26,28, 29,31
A	ZHU, XI ET AL: "Trp, A novel mammalian gene family essential for agonist-activated capacitative Ca-2+ entry." CELL, vol. 85, no. 5, 1996, pages 661-671, XP000907242 page 662 page 665 figures 1,5,6 ---	20,21, 25,26, 28,29,31
A	GARCIA REYNALDO L ET AL: "Differential expression of mammalian TRP homologues across tissues and cell lines." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS 1997, vol. 239, no. 1, 1997, pages 279-283, XP002138822 ISSN: 0006-291X See Materials and Methods figure 1 --- -/-	25,26, 28-30

INTERNATIONAL SEARCH REPORT

In ternational Application No
PCT/US 99/29996

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SINKINS WILLIAM G ET AL: "Functional expression of TrpC1: A human homologue of the Drosophila Trp channel." BIOCHEMICAL JOURNAL APRIL, 1998, vol. 331, no. 1, April 1998 (1998-04), pages 331-339, XP000864583 ISSN: 0264-6021 page 333-335; figures 3-5	24
A	PREUSS KLAUS-DIETER ET AL: "Expression and characterization of a trp1 homolog from rat." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS NOV. 7, 1997, vol. 240, no. 1, 7 November 1997 (1997-11-07), pages 167-172, XP002138821 ISSN: 0006-291X figure 2	24
A	OBUKHOV, ALEXANDER G. ET AL: "Direct activation of trp1 cation channels by G-alpha-11 subunits." EMBO (EUROPEAN MOLECULAR BIOLOGY ORGANIZATION) JOURNAL, (1996) VOL. 15, NO. 21, PP. 5833-5838., XP000907243 figure 2	24
P,X	WO 99 09199 A (RYAZANOV ALEXEY G ;PAVUR KAREN S (US); HAIT WILLIAM N (US); UNIV M) 25 February 1999 (1999-02-25) see melanome kinase polynucleotide and polypeptide sequences on page 16-17	1,3, 10-19, 25-36
P,X	WO 99 09166 A (SHAPERO MICHAEL H ;DENDREON CORP (US); LAUS REINER (US); TSAVALER) 25 February 1999 (1999-02-25) page 17, line 24 -page 18, line 9 page 25, line 19-32 page 28, line 1-4 SEQ ID NOs: 27, 28 and 31.	1,5-19, 25-35
T	SCHARENBERG A M ET AL: "MLSN-1/SOC-1 defines a widely expressed Ca2+/cation channel family involved in Ca2+ homeostasis and store-operated Ca2+ signaling." FIFTY-THIRD ANNUAL MEETING OF THE SOCIETY OF GENERAL PHYSIOLOGISTS;WOODS HOLE, MASSACHUSETTS, USA; SEPTEMBER 9-11, 1999, vol. 114, no. 1, July 1999 (1999-07), page 14a XP000910708 Journal of General Physiology July, 1999 ISSN: 0022-1295	

INTERNATIONAL SEARCH REPORT

...ernational application No.
PCT/US 99/29996

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,
no additional fees are to be refunded.

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
1-36
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-5, 10-13, 16-19, 32-35 relate to an extremely large number of possible polynucleotides, polypeptides encoded by them, binding polypeptides, and kits and pharmaceutical compositions containing said polypeptides and polynucleotides. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the polynucleotide of SEQ ID NOs: 1, 27, 29 and 31 and the corresponding polypeptide of SEQ ID NOs: 2, 28, 30 and 32.

Present claims 16 and 17 relate to an extremely large number of possible compounds, namely, a polypeptide that binds to the polypeptide of the invention. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to an antibody, antibody fragment, F(ab)2 fragment or a fragment including a CDR3 region selective for the polypeptides of the invention.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1, 6-36 (partially) and 2 (complete)

An isolated nucleic acid molecule comprising a nucleic acid molecule that hybridizes to a nucleic acid molecule of SEQ ID NO:1 and which code for a SOC/CRAC polypeptide, nucleic acid molecules that differ in codon sequence due to degeneracy of the genetic code and complement thereof, polynucleotides which are not identical to the SEQ ID or sequences of GenBank accession number of Table 1; expression vector, host cells; polypeptide encoded thereof (SEQ ID NO:2); polypeptides binding to the polypeptide of SEQ ID NO:2, including antibodies; kits comprising agents that selectively bind to the polynucleotide (SEQ ID NO:1) or polypeptide (SEQ ID NO:2) of the invention; pharmaceutical compositions containing the polynucleotide or polypeptides of the invention; a method for isolating the SOC/CRAC molecule having SOC/CRAC calcium channel activity comprising contacting a binding molecule that is SOC/CRAC nucleic acid or a SOC/CRAC binding polypeptide with a sample containing SOC/CRAC molecules allowing the formation of the complex, detecting the formation of the complex, isolating the SOC/CRAC molecule and determining whether the isolated SOC/CRAC molecule has SOC/CRAC calcium channel activity; a method for identifying agents useful in the modulation of SOC/CRAC calcium channel activity; a method to determine the level of SOC/CRAC expression in a subject, including expression of SOC/CRAC polypeptide or mRNA in a tissue or biological fluid sample using PCR, Northern blotting, and mono- and polyclonal antisera and a method for identifying agents useful in the modulation of the SOC/CRAC polypeptide kinase activity, comprising the use of aminoacids 999-1180 from SEQ ID NO:4 as a candidate kinase.

2. Claims: 1,6-36 (partially)

As subject 1, but referred to the polynucleotide of SEQ ID NO:3 and to the encoded polypeptide of SEQ ID NO:4

3. Claims: 1,6-36 (partially)

As subject 1, but referred to the polynucleotide of SEQ ID NO:5 and to the encoded polypeptide of SEQ ID NO:6

4. Claims: 1,6-36 (partially)

As subject 1, but referred to the polynucleotide of SEQ ID NO:7 and to the encoded polypeptide of SEQ ID NO:8

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

5. Claims: 1,6-36 (partially) and 37 (complete)

As subject 1, but referred to the polynucleotide of SEQ ID NO:23 and to the encoded polypeptide of SEQ ID NO:24

6. Claims: 1,6-36 (partially)

As subject 1, but referred to the polynucleotide of SEQ ID NO:25 and to the encoded polypeptide of SEQ ID NO:26

7. Claims: 1,10-36 (partially) and 3 (complete)

As subject 1, but referred to the polynucleotide of SEQ ID NO:27 and to the encoded polypeptide of SEQ ID NO:28

8. Claims: 1,6-36 (partially) and 4 (complete)

As subject 1, but referred to the polynucleotide of SEQ ID NO:29 and to the encoded polypeptide of SEQ ID NO:30

9. Claims: 1,6-36 (partially) and 5 (complete)

As subject 1, but referred to the polynucleotide of SEQ ID NO:31 and to the encoded polypeptide of SEQ ID NO:32.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ternational Application No

PCT/US 99/29996

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9815657 A	16-04-1998	US 5919638 A EP 0954599 A US 6110675 A	06-07-1999 10-11-1999 29-08-2000
WO 9837093 A	27-08-1998	AU 6181898 A CN 1252837 T EP 1005546 A NO 994069 A PL 335348 A ZA 9801585 A	09-09-1998 10-05-2000 07-06-2000 22-10-1999 25-04-2000 04-09-1998
WO 9909199 A	25-02-1999	AU 9110098 A	08-03-1999
WO 9909166 A	25-02-1999	AU 9021898 A EP 1005549 A	08-03-1999 07-06-2000

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 July 2000 (13.07.2000)

PCT

(10) International Publication Number
WO 00/40614 A3

(51) International Patent Classification⁷: C07K 14/705,
C12N 15/12, C12Q 1/68, C12N 5/10, C07K 16/28, G01N
33/53, A61K 38/17

(74) Agent: PLUMER, Elizabeth, R.; Wolf, Greenfield &
Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210 (US).

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NL, PT, SE).

(25) Filing Language: English

Published:

(26) Publication Language: English

— with international search report

(30) Priority Data:
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60/120,018 29 January 1999 (29.01.1999) US
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(88) Date of publication of the international search report:
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(48) Date of publication of this corrected version:
30 August 2001

(71) Applicant (*for all designated States except US*): BETH
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[US/US]; 1 Deaconess Road, Boston, MA 02215 (US).

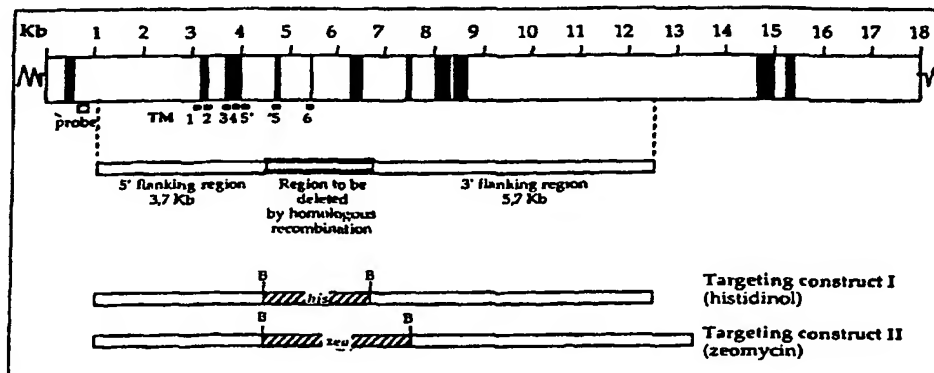
(15) Information about Correction:
see PCT Gazette No. 35/2001 of 30 August 2001, Section
II

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(54) Title: CHARACTERIZATION OF THE SOC/CRAC CALCIUM CHANNEL PROTEIN FAMILY



(57) Abstract: Nucleic acids encoding SOC/CRAC calcium channel polypeptides, including fragments and biologically functional variants thereof and encoded polypeptides are provided. The nucleic acids and polypeptides disclosed herein are useful as therapeutic and diagnostic agents. Agents that selectively bind to the foregoing polypeptides and genes also are provided.



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CHARACTERIZATION OF A CALCIUM CHANNEL FAMILY**Field of the Invention**

This invention relates to nucleic acids coding for a novel family of calcium channel polypeptides, the encoded polypeptides, unique fragments of the foregoing, and methods of making and using same.

Background of the Invention

Calcium channels are membrane-spanning, multi-subunit proteins that facilitate the controlled transport ("flux") of Ca^{2+} ions into and out of cells. Cells throughout the animal kingdom, and at least some bacterial, fungal and plant cells, possess one or more types of calcium channels. In general, "excitable" cells, such as neurons of the central nervous system, peripheral nerve cells, and muscle cells, including those of skeletal muscles, cardiac muscles, and venous and arterial smooth muscles, possess voltage-dependent calcium channels. In a voltage-dependent calcium channel, the transport of Ca^{2+} ions into and out of the cells requires a certain minimal level of depolarization (the difference in potential between the inside of the cell bearing the channel and the extracellular environment) with the rate of Ca^{2+} cell flux dependent on the difference in potential. In "non-excitable" cells, calcium influx is thought to occur predominantly in response to stimuli which cause the release of calcium from intracellular stores. This process, termed *store operated calcium influx*, is not well understood.

Characterization of a particular type of calcium channel by analysis of whole cells is complicated by the presence of mixed populations of different types of calcium channels in the majority of cells. Although single-channel recording methods can be used to examine individual calcium channels, such analysis does not reveal information related to the molecular structure or biochemical composition of the channel. Furthermore, in this type of analysis, the channel is isolated from other cellular constituents that might be important for the channel's natural functions and pharmacological interactions. To study the calcium channel structure-function relationship, large amounts of pure channel protein are needed. However, acquiring large amounts of pure protein is difficult in view of the complex nature of these multisubunit proteins, the varying concentrations of calcium channel proteins in tissue sources, the presence of mixed populations of calcium channel proteins in tissues, and the modifications of the native protein that can occur during the isolation procedure.

Summary of the Invention

The invention is based on the identification of a novel family of calcium channel polypeptides and the molecular cloning and partial characterization of a novel member of this family that is expressed predominantly in human hematopoietic cells, liver, and kidney. This newly identified family of calcium channel polypeptides is designated, "SOC" or "CRAC" or "ICRAC", for Store Operated Channels or Calcium Release Activated Channels. Although not wishing to be bound to any particular theory or mechanism, it is believed that the SOC/CRAC calcium channel polypeptides are transmembrane polypeptides that modulate Ca^{2+} flux "into" and "out of" a cell, for example, in certain instances they may be activated upon depletion of Ca^{2+} from intracellular calcium stores, allowing Ca^{2+} influx into the cell. Accordingly, the compositions disclosed herein are believed to be useful for modulating calcium transport into and out of such intracellular stores and for the treatment of disorders that are characterized by aberrant calcium transport into and out of such intracellular stores. In particular, we believe that the SOC/CRAC calcium channel polypeptides disclosed herein play an important role in the influx of extracellular calcium by mediating the refilling of intracellular calcium stores following their depletion. Accordingly, we believe that the compositions for expressing functional SOC/CRAC calcium channel polypeptides in cells, as disclosed herein, are useful for treating patients having conditions that are characterized by reduced extracellular calcium influx into their SOC/CRAC-expressing cells. Additionally, the compositions of the invention are useful for delivering therapeutic and/or imaging agents to cells which preferentially express SOC/CRAC calcium channel polypeptides and, in particular, for delivering such agents to hematopoietic cells, liver, heart, spleen, and kidney to modulate proliferation and growth of these cells. Moreover, in view of the importance of cellular calcium levels to cell viability, we believe that SOC-2/CRAC-1, SOC-3/CRAC-2, and SOC-4/CRAC-3 as disclosed herein, and/or other members of the SOC/CRAC family of calcium channel polypeptides, represent an ideal target for designing and/or identifying (e.g., from molecular libraries) small molecule inhibitors that block lymphocyte proliferation, as well as other binding agents that selectively bind to SOC/CRAC polypeptides to which drugs or toxins can be conjugated for delivery to SOC/CRAC polypeptide expressing cells.

The invention is based, in part, on the molecular cloning and sequence analysis of the novel SOC/CRAC calcium channel molecules disclosed herein (also referred to as a "SOC-2/CRAC-1 molecule," a "SOC-3/CRAC-2 molecule," and/or "SOC-4/CRAC-3 molecule") that are predominantly expressed in human hematopoietic cells, liver, spleen, heart, and

kidney (SOC-2/CRAC-1), kidney and colon (SOC-3/CRAC-2), and prostate (SOC-4/CRAC-3 molecule). As used herein, a "SOC/CRAC molecule" embraces a "SOC/CRAC calcium channel nucleic acid" (or "SOC/CRAC nucleic acid") and a "SOC/CRAC calcium channel polypeptide" (or "SOC/CRAC polypeptide"). Homologs and alleles also are embraced within
5 the meaning of a SOC/CRAC calcium channel molecule.

According to one aspect of the invention, isolated SOC/CRAC nucleic acids which code for one or more member(s) of the SOC/CRAC family of calcium channel polypeptides or unique fragments thereof are provided. The isolated nucleic acids refer to one or more of the following:

10 (a) nucleic acid molecules which hybridize under stringent conditions to a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, and which code for a SOC/CRAC polypeptide;

(b) deletions, additions and substitutions of (a) which code for a respective
15 SOC/CRAC polypeptide;

(c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) in codon sequence due to the degeneracy of the genetic code, and

(d) complements of (a), (b) or (c).

The invention in another aspect provides an isolated nucleic acid molecule selected
20 from the group consisting of (a) a unique fragment of a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:29, and SEQ ID NO:31, (b) complements of (a), provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to any sequence selected from a sequence group consisting of (1) sequences having
25 the SEQ. ID NOS. or GenBank accession numbers of Table I, (2) complements of (1), and (3) fragments of (1) and (2).

According to yet another aspect of the invention, isolated SOC/CRAC polypeptides are provided. The isolated SOC/CRAC polypeptide molecules are encoded by one or more SOC/CRAC nucleic acid molecules of the invention. Preferably, the SOC/CRAC polypeptide
30 contains one or more polypeptides selected from the group consisting of the polypeptides having SEQ. ID Nos. 2, 4, 6, 8, 24, 26, 28, 30, and 32. In other embodiments, the isolated polypeptide may be a fragment or variant of the foregoing SOC/CRAC polypeptide molecules of sufficient length to represent a sequence unique within the human genome, and identifying

with a polypeptide that functions as a calcium channel, provided that the fragment excludes a sequence of contiguous amino acids identified in Table II, and/or excludes a sequence of contiguous amino acids encoded for by a nucleic acid sequence identified in Table I. In another embodiment, immunogenic fragments of the polypeptide molecules described above are provided.

According to another aspect of the invention, isolated SOC/CRAC binding agents (e.g., polypeptides) are provided which selectively bind to a SOC/CRAC molecule (e.g., a SOC/CRAC polypeptide encoded by the isolated nucleic acid molecules of the invention). Preferably, the isolated binding agents selectively bind to a polypeptide which comprises the sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32, or unique fragments thereof. In the preferred embodiments, the isolated binding polypeptides include antibodies and fragments of antibodies (e.g., Fab, F(ab)₂, Fd and antibody fragments which include a CDR3 region which binds selectively to a SOC/CRAC polypeptide). Preferably, the antibodies for human therapeutic applications are human antibodies.

According to another aspect of the invention, a pharmaceutical composition containing a pharmaceutically effective amount of an isolated SOC/CRAC nucleic acid, an isolated SOC/CRAC polypeptide, or an isolated SOC/CRAC binding polypeptide in a pharmaceutically acceptable carrier also is provided. The pharmaceutical compositions are useful in accordance with therapeutic methods disclosed herein.

According to yet another aspect of the invention, a method for isolating a SOC/CRAC molecule is provided. The method involves:

a) contacting a SOC/CRAC nucleic acid or a SOC/CRAC binding polypeptide with a sample that is believed to contain one or more SOC/CRAC molecules, under conditions to form a complex of the SOC/CRAC nucleic acid or the SOC/CRAC binding polypeptide and the SOC/CRAC molecule;

b) detecting the presence of the complex;

c) isolating the SOC/CRAC molecule from the complex; and

d) determining whether the isolated SOC/CRAC molecule has SOC/CRAC calcium channel activity. As used herein "SOC/CRAC calcium channel activity" refers to the transport of Ca²⁺ into and out of intracellular stores that is mediated by a SOC/CRAC

polypeptide. In general, the SOC/CRAC calcium channel activity is initiated by a reduction or depletion of intracellular calcium stores.

In certain embodiments, the SOC/CRAC nucleic acid is a SOC-2/CRAC-1 nucleic acid (e.g., a nucleic acid having SEQ. ID NO. 27, or complements thereof); in certain other
5 embodiments, the SOC/CRAC nucleic acid is a SOC-3/CRAC-2 nucleic acid (e.g., a nucleic acid having SEQ. ID NO. 29, or complements thereof); in further embodiments, the SOC/CRAC nucleic acid is a SOC-4/CRAC-3 nucleic acid (e.g., a nucleic acid having SEQ. ID NO. 31, or complements thereof). In yet other embodiments, the SOC/CRAC polypeptide is a SOC-2/CRAC-1 binding polypeptide (e.g., an antibody that selectively binds to a SOC-
10 2/CRAC-1 polypeptide). In yet further embodiments, the SOC/CRAC polypeptide is a SOC-3/CRAC-2 binding polypeptide (e.g., an antibody that selectively binds to a SOC-3/CRAC-2 polypeptide). In some embodiments, the SOC/CRAC polypeptide is a SOC-4/CRAC-3 binding polypeptide (e.g., an antibody that selectively binds to a SOC-4/CRAC-3 polypeptide). In the preferred embodiments, the isolated binding polypeptides include
15 antibodies and fragments of antibodies (e.g., Fab, F(ab)₂, Fd and antibody fragments which include a CDR3 region which binds selectively to a SOC-2/CRAC-1, to a SOC-3/CRAC-2, and/or to a SOC-4/CRAC-3 polypeptide). Preferably the isolated binding polypeptides or other binding agents selectively bind to a single SOC/CRAC molecule, i.e., are capable of distinguishing between different members of the SOC/CRAC family. Accordingly, one or
20 more SOC/CRAC binding agents can be contained in a single composition (e.g., a pharmaceutical composition) to identify multiple SOC/CRAC molecules *in vivo* or *in vitro*.

According to yet another aspect of the invention, a method for identifying agents useful in the modulation of SOC/CRAC calcium channel activity is provided. The method involves:

25 a) contacting a SOC/CRAC polypeptide with a candidate agent suspected of modulating SOC/CRAC calcium channel activity, under conditions sufficient to allow the candidate agent to interact selectively with (e.g. bind to) the SOC/CRAC polypeptide;

 b) detecting a Ca²⁺ concentration of step (b) associated with the SOC/CRAC calcium channel activity of the SOC/CRAC polypeptide in the presence of the candidate agent; and

30 c) comparing the Ca²⁺ concentration of step (b) with a control Ca²⁺ concentration of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the candidate agent modulates (increases or decreases) SOC/CRAC calcium channel activity.

According to another aspect of the invention, a method for identifying agents useful in the modulation of a SOC/CRAC polypeptide kinase activity is provided. The method involves:

a) contacting a SOC/CRAC polypeptide with kinase activity with a candidate agent suspected of modulating SOC/CRAC kinase activity, under conditions sufficient to allow the candidate agent to interact with the SOC/CRAC polypeptide and modulate its kinase activity;

b) detecting a kinase activity associated with the SOC/CRAC polypeptide in the presence of the candidate agent; and

c) comparing the kinase activity of step (b) with a control kinase activity of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the candidate agent modulates (increases or decreases) SOC/CRAC kinase activity. In some embodiments the SOC/CRAC polypeptide comprises amino acids 999-1180 of the SOC-2/CRAC-1 polypeptide (SEQ ID NO:24), or a fragment thereof that retains the kinase activity.

According to yet another aspect of the invention, a method for determining the level of expression of a SOC/CRAC polypeptide in a subject is provided. The method involves:

a) measuring the expression of a SOC/CRAC polypeptide in a test sample, and

b) comparing the measured expression of the SOC/CRAC polypeptide in the test sample to the expression of a SOC/CRAC polypeptide in a control containing a known level of expression to determine the level of SOC/CRAC expression in the subject. Expression is defined as SOC/CRAC mRNA expression or SOC/CRAC polypeptide expression. Various methods can be used to measure expression. The preferred embodiments of the invention utilize PCR and Northern blotting for measuring mRNA expression, and monoclonal or polyclonal SOC/CRAC antisera as reagents for measuring SOC/CRAC polypeptide expression. In preferred embodiments, the SOC/CRAC molecule (nucleic acid and/or polypeptide) is SOC-2/CRAC-1. In other preferred embodiments, the SOC/CRAC molecule is SOC-3/CRAC-2. In yet further preferred embodiments, the SOC/CRAC molecule is SOC-4/CRAC-3. In certain embodiments, the test samples include biopsy samples and biological fluids such as blood. The method is useful, e.g., for assessing the presence or absence or stage of a proliferative disorder in a subject.

The invention also contemplates kits comprising a package including assays for SOC/CRAC epitopes, SOC/CRAC nucleic acids, and instructions, and optionally related materials such as controls, for example, a number, color chart, or an epitope of the expression product of the foregoing isolated nucleic acid molecules of the invention for comparing, for

example, the level of SOC/CRAC polypeptides or SOC/CRAC nucleic acid forms (wild-type or mutant) in a test sample to the level in a control sample having a known amount of a SOC/CRAC nucleic acid or SOC/CRAC polypeptide. This comparison can be used to assess in a subject a risk of developing a cancer or the progression of a cancer. The kits may also include assays for other known genes, and expression products thereof, associated with, for example, proliferative disorders (e.g., BRCA, p53, etc.). In a preferred embodiment, the kit comprises a package containing: (a) a binding agent that selectively binds to an isolated nucleic acid of the invention or an expression product thereof to obtain a measured test value, (b) a control containing a known amount of a SOC/CRAC nucleic acid or a SOC/CRAC polypeptide to obtain a measured control value, and (c) instructions for comparing the measured test value to the measured control value to determine the amount of SOC/CRAC nucleic acid or expression product thereof in a sample.

The invention provides isolated nucleic acid molecules, unique fragments thereof, expression vectors containing the foregoing, and host cells containing the foregoing. The invention also provides isolated binding polypeptides and binding agents which bind such polypeptides, including antibodies, and pharmaceutical compositions containing any of the compositions of the invention. The foregoing can be used, *inter alia*, in the diagnosis or treatment of conditions characterized by the aberrant expression levels and/or the presence of mutant forms of a SOC/CRAC nucleic acid or polypeptide. The invention also provides methods for identifying agents that alter the function of the SOC/CRAC polypeptide.

These and other aspects of the invention, as well as various advantages and utilities, will be more apparent with reference to the detailed description of the preferred embodiments.

Brief Description of the Sequences

SEQ ID NO:1 is a partial nucleotide sequence of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:2 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:1).

SEQ ID NO:3 is a partial nucleotide sequence of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:4 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:3).

SEQ ID NO:5 is a partial nucleotide sequence of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:6 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:5).

-8-

SEQ ID NO:7 is a partial nucleotide sequence of the mouse homologue (mSOC-2/CRAC-1) of the human SOC-2/CRAC-1 cDNA.

SEQ ID NO:8 is the predicted amino acid sequence of the translation product of the mSOC-2/CRAC-1 cDNA (SEQ ID NO:7).

5 SEQ ID NO:9 is the nucleotide sequence of the mouse MLSN-1 (SOC-1) cDNA.

SEQ ID NO:10 is the predicted amino acid sequence of the translation product of the mouse MLSN-1 (SOC-1) cDNA (SEQ ID NO:9).

SEQ ID NO:11 is the nucleotide sequence of a human calcium channel cDNA with GenBank Acc. no.: AB001535.

10 SEQ ID NO:12 is the predicted amino acid sequence of the translation product of the human calcium channel cDNA with GenBank Acc. no.: AB001535 (SEQ ID NO:11).

SEQ ID NO:13 is the amino acid sequence of a *C. Elegans* polypeptide at the c05c12.3 locus.

15 SEQ ID NO:14 is the amino acid sequence of a *C. Elegans* polypeptide at the F54D1 locus.

SEQ ID NO:15 is the amino acid sequence of a *C. Elegans* polypeptide at the t01H8 locus.

SEQ ID NO:16 is the nucleotide sequence of a mouse kidney cDNA with GenBank Acc. no.: AI226731.

20 SEQ ID NO:17 is the predicted amino acid sequence of the translation product of the mouse kidney cDNA with GenBank Acc. no.: AI226731 (SEQ ID NO:16).

SEQ ID NO:18 is the nucleotide sequence of a human brain cDNA with GenBank Acc. no.: H18835.

25 SEQ ID NO:19 is the predicted amino acid sequence of the translation product of the human brain cDNA with GenBank Acc. no.: H18835 (SEQ ID NO:18).

SEQ ID NO:20 is the nucleotide sequence of the human EST with GenBank Acc. no.: AA419592.

SEQ ID NO:21 is the nucleotide sequence of the human EST with GenBank Acc. no.: AA419407.

30 SEQ ID NO:22 is the nucleotide sequence of the mouse EST with GenBank Acc. no.: AI098310.

SEQ ID NO:23 is a partial nucleotide sequence of the human SOC-2/CRAC-1 cDNA that contains the SOC-2/CRAC-1 sequences of SEQ ID NO:1, SEQ ID NO:3, and SEQ ID NO:5.

5 SEQ ID NO:24 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:23).

SEQ ID NO:25 is a partial nucleotide sequence of the human SOC-3/CRAC-2 cDNA.

SEQ ID NO:26 is the predicted amino acid sequence of the translation product of human SOC-3/CRAC-2 cDNA (SEQ ID NO:25).

SEQ ID NO:27 is the full nucleotide sequence of the human SOC-2/CRAC-1 cDNA.

10 SEQ ID NO:28 is the predicted amino acid sequence of the translation product of human SOC-2/CRAC-1 cDNA (SEQ ID NO:27).

SEQ ID NO:29 is the full nucleotide sequence of the human SOC-3/CRAC-2 cDNA.

SEQ ID NO:30 is the predicted amino acid sequence of the translation product of human SOC-3/CRAC-2 cDNA (SEQ ID NO:29).

15 SEQ ID NO:31 is the full nucleotide sequence of the human SOC-4/CRAC-3 cDNA.

SEQ ID NO:32 is the predicted amino acid sequence of the translation product of human SOC-4/CRAC-3 cDNA (SEQ ID NO:31).

Brief Description of the Drawings

20 Figure 1 is a schematic depicting the intron/exon organization of the chicken SOC-2/CRAC-1 genomic sequence, as well as the putative transmembrane (TM) domains, and the targeting constructs utilized in the knockout experiments.

Detailed Description of the Invention

One aspect of the invention involves the partial cloning of cDNAs encoding members of a novel family of calcium channel polypeptides, referred to herein as "SOC/CRAC" (designated "SOC" or "CRAC" or "ICRAC", for Sore Operated Channels or Calcium Release Activated Channels, or CECH). Although not intending to be bound to any particular mechanism or theory, we believe that a SOC/CRAC family member is a transmembrane calcium channel that modulates Ca^{2+} flux "into" and "out of" a cell; in certain instances it may be activated upon depletion of Ca^{2+} from intracellular calcium stores, allowing Ca^{2+} influx into the cell.

30 The first three isolated SOC/CRAC members disclosed herein, define a new family of calcium channels which is distinct from previously described calcium channels, such as voltage gated calcium channels, ryanodine receptor/inositol-1,4,5-triphosphate receptor

channels, and Transient Receptor Potential (TRP) channels. The SOC/CRAC family of calcium channels exhibits high selectivity (with a P_{Ca}/P_{Na} ratio near 1000), a unitary conductance below the detection level of the patch clamp method (the conductance estimated at approximately 0.2 picosiemens), and are subject to inhibition by high intracellular calcium levels. Although not intending to be bound to any particular mechanism or theory, we believe that SOC/CRAC calcium channels are responsible for the majority of, for example, calcium entry which occurs when intracellular calcium stores are depleted, and that SOC/CRAC currents are important for initiating various types of calcium-dependent processes. Thus, we believe that SOC/CRAC calcium channels play an important role in cellular calcium homeostasis by, e.g., modulating the supply of calcium to refill intracellular stores when depleted.

The isolated full-length sequence of a representative, first member of the SOC/CRAC family, human SOC/CRAC nucleic acid (cDNA), SOC-2/CRAC-1, is represented as the nucleic acid of SEQ ID NO:27. This nucleic acid sequence codes for the SOC-2/CRAC-1 polypeptide with the predicted amino acid sequence disclosed herein as SEQ ID NO:28. A homologous mouse cDNA sequence (>90% identity to the human at the nucleotide level) is represented as the nucleic acid of SEQ ID NO:7, and codes for a unique fragment of a mouse SOC-2/CRAC-1 polypeptide having the predicted, partial amino acid sequence represented as SEQ ID NO:8. Analysis of the SOC-2/CRAC-1 partial sequence by comparison to nucleic acid and protein databases show that SOC-2/CRAC-1 shares a limited homology to mouse MLSN-1 (SOC-1, SEQ ID NOs: 9 and 10). Limited homology is also shared between SOC-2/CRAC-1 and three *C. Elegans* polypeptides (SEQ ID NOs: 13, 14, and 15). We further believe that SOC-2/CRAC-1 plays a role in the regulation of cellular Ca^{2+} fluxing and, in particular, lymphocyte Ca^{2+} fluxing.

A second member of the human SOC/CRAC family of calcium channels, SOC-3/CRAC-2, is represented as the nucleic acid of SEQ ID NO:29, and codes for the human SOC-3/CRAC-2 polypeptide having the predicted amino acid sequence represented as SEQ ID NO:30 (this molecule may also be referred to as CECH2). SOC-3/CRAC-2 is predominantly expressed in human hematopoietic cells (including peripheral blood lymphocytes, liver, bone marrow, spleen, thymus, lymph nodes, heart, and kidney. Expression can also be detected (at lesser levels) in brain, skeletal muscle colon, small intestine, placenta, lung, and cells (cell lines) such as HL-60, HeLa, K562, MOLT-4, SW-480, A459, and G361.

A third member of the human SOC/CRAC family of calcium channels, SOC-4/CRAC-3, is represented as the nucleic acid of SEQ ID NO:31, and codes for the human SOC-4/CRAC-3 polypeptide having the predicted amino acid sequence represented as SEQ ID NO:32 (this molecule may also be referred to as CECH6). It specifically expressed in the prostate gland/cells.

As used herein, a SOC/CRAC calcium channel nucleic acid (also referred to herein as a "SOC/CRAC nucleic acid" refers to a nucleic acid molecule which: (1) hybridizes under stringent conditions to one or more of the nucleic acids having the sequences of SEQ. ID NOS. 7, 27, 29, and/or 31 (sequences of the mouse and human SOC-2/CRAC-1, human SOC-3/CRAC-2, and human SOC-4/CRAC-3 nucleic acids), and (2) codes for a SOC-2/CRAC-1, a SOC-3/CRAC-2 or a SOC-4/CRAC-3 calcium channel polypeptide, respectively, or unique fragments of said SOC-2/CRAC-1, SOC-3/CRAC-2, or SOC-4/CRAC-3 polypeptide.

As used herein, a SOC/CRAC calcium channel polypeptide (also referred to herein as a "SOC/CRAC polypeptide") refers to a polypeptide that is coded for by a SOC-2/CRAC-1, a SOC-3/CRAC-2, and/or a SOC-4/CRAC-3 nucleic acid. Preferably, the above-identified SOC/CRAC polypeptides mediate transport of calcium into and out of a cell.

SOC/CRAC polypeptides also are useful as immunogenic molecules for the generation of binding polypeptides (e.g., antibodies) which bind selectively to SOC/CRAC (e.g., SOC-2/CRAC-1, SOC-3/CRAC-2, and/or SOC-4/CRAC-3) polypeptides. Such antibodies can be used in diagnostic assays to identify and/or quantify the presence of a SOC/CRAC polypeptide in a sample, such as a biological fluid or biopsy sample. SOC/CRAC polypeptides further embrace functionally equivalent fragments, variants, and analogs of the preferred SOC/CRAC polypeptides, provided that the fragments, variants, and analogs also are useful in mediating calcium transport into and out of intracellular calcium stores.

As used herein, "SOC/CRAC calcium channel activity" refers to Ca^{2+} transport ("Ca²⁺ fluxing") across the plasma membrane that is mediated by a SOC/CRAC calcium channel polypeptide. The SOC/CRAC calcium channel polypeptide typically has one or more of the following properties: high selectivity, a unitary conductance below the detection level of the patch clamp method, and are subject to inhibition by high intracellular calcium levels. Such activity can be easily detected using standard methodology well known in the art. See, e.g., the Examples and Neher, E., "Ion channels for communication between and within cells",

Science, 1992; 256:498-502; and Hoth, M., and Penner, R., "Depletion of intracellular calcium stores activates a calcium current in mast cells", Nature, 1992; 355 (6358):353-6.

According to one aspect of the invention, isolated nucleic acid molecules which code for one or more member(s) of the SOC/CRAC family of calcium channel polypeptides are provided. The isolated nucleic acid molecules are selected from the following groups:

(a) nucleic acid molecules which hybridize under stringent conditions to one or more nucleic acid molecules selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, and which code for a SOC/CRAC polypeptide;

(b) deletions, additions and substitutions of (a) which code for a respective SOC/CRAC polypeptide;

(c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) in codon sequence due to the degeneracy of the genetic code, and

(d) complements of (a), (b) or (c).

In certain embodiments, the isolated nucleic acid molecule comprises one or more of nucleotides 1-1212 of SEQ ID NO:1; nucleotides 1-739 of SEQ ID NO:3; nucleotides 1-1579 of SEQ ID NO:5; nucleotides 1-5117 of SEQ ID NO:23; the mouse homolog for SOC-2/CRAC-1 corresponding to SEQ ID NO:7; nucleotides 1-2180 of SEQ ID NO:25; nucleotides 382-5976 of SEQ ID NO:27; nucleotides 73-3714 of SEQ ID NO:29; and nucleotides 23-3434 of SEQ ID NO:31. In yet other embodiments, the isolated nucleic acid molecule comprises a molecule which encodes a polypeptide having one or more sequences selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32.

According to yet another aspect of the invention, an isolated nucleic acid molecule is provided which is selected from the group consisting of:

(a) a unique fragment of a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, (of sufficient length to represent a sequence unique within the human genome); and (b) complements of (a), provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to a sequence in the prior art as represented by the sequence group consisting of: (1) sequences having the SEQ ID NOs or GenBank accession numbers of Table I, (2) complements of (1), and (3) fragments of (1) and (2).

In some embodiments, the sequence of contiguous nucleotides is selected from the group consisting of (1) at least two contiguous nucleotides nonidentical to the sequence group, (2) at least three contiguous nucleotides nonidentical to the sequence group, (3) at least four contiguous nucleotides nonidentical to the sequence group, (4) at least five contiguous
5 nucleotides nonidentical to the sequence group, (5) at least six contiguous nucleotides nonidentical to the sequence group, (6) at least seven contiguous nucleotides nonidentical to the sequence group.

In other embodiments, the unique fragment has a size selected from the group consisting of at least: 8 nucleotides, 10 nucleotides, 12 nucleotides, 14 nucleotides, 16
10 nucleotides, 18 nucleotides, 20, nucleotides, 22 nucleotides, 24 nucleotides, 26 nucleotides, 28 nucleotides, 30 nucleotides, 40 nucleotides, 50 nucleotides, 75 nucleotides, 100 nucleotides, 200 nucleotides, 1000 nucleotides and every integer length therebetween.

According to another aspect of the invention, expression vectors and host cells containing (e.g., transformed or transfected with) expression vectors comprising the nucleic
15 acid molecules disclosed herein operably linked to a promoter are provided. In certain preferred embodiments, the host cells are eukaryotic cells.

The isolated nucleic acid molecules disclosed herein have various utilities, including their use as probes and primers to identify additional members of the SOC/CRAC family of calcium channels, as diagnostic reagents for identifying the presence of SOC/CRAC
20 polypeptides in biological or other samples, and as agents for generating SOC/CRAC binding polypeptides (e.g., antibodies) that can be used as reagents in diagnostic and therapeutic assays to identify the presence, absence, and/or amounts of a SOC/CRAC nucleic acid or polypeptide in a biological or other sample.

As used herein with respect to nucleic acids, the term "isolated" means: (i) amplified
25 *in vitro* by, for example, polymerase chain reaction (PCR); (ii) recombinantly produced by cloning; (iii) purified, as by cleavage and gel separation; or (iv) synthesized by, for example, chemical synthesis. An isolated nucleic acid is one which is readily manipulatable by recombinant DNA techniques well known in the art. Thus, a nucleotide sequence contained in a vector in which 5' and 3' restriction sites are known or for which polymerase chain
30 reaction (PCR) primer sequences have been disclosed is considered isolated but a nucleic acid sequence existing in its native state in its natural host is not. An isolated nucleic acid may be substantially purified, but need not be. For example, a nucleic acid that is isolated within a cloning or expression vector is not pure in that it may comprise only a tiny percentage of the

material in the cell in which it resides. Such a nucleic acid is isolated, however, as the term is used herein because it is readily manipulatable by standard techniques known to those of ordinary skill in the art.

As used herein with respect to polypeptides (discussed below), the term "isolated" means separated from its native environment in sufficiently pure form so that it can be manipulated or used for any one of the purposes of the invention. Thus, isolated means sufficiently pure to be used (i) to raise and/or isolate antibodies, (ii) as a reagent in an assay, or (iii) for sequencing, etc.

Homologs and alleles of the SOC/CRAC nucleic acids of the invention can be identified by conventional techniques. Thus, an aspect of the invention is those nucleic acid sequences which code for SOC/CRAC polypeptides and which hybridize to a nucleic acid molecule selected from a group consisting of the nucleic acid of SEQ ID NO:1, the nucleic acid of SEQ ID NO:3, the nucleic acid of SEQ ID NO:5, the nucleic acid of SEQ ID NO:7, the nucleic acid of SEQ ID NO:23, the nucleic acid of SEQ ID NO:25, the nucleic acid of SEQ ID NO:27, the nucleic acid of SEQ ID NO:29, and the nucleic acid of SEQ ID NO:31, under stringent conditions. The term "stringent conditions" as used herein refers to parameters with which the art is familiar. Nucleic acid hybridization parameters may be found in references which compile such methods, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. More specifically, stringent conditions, as used herein, refers, for example, to hybridization at 65°C in hybridization buffer (3.5 x SSC, 0.02% Ficoll, 0.02% polyvinyl pyrrolidone, 0.02% Bovine Serum Albumin, 2.5mM NaH₂PO₄(pH7), 0.5% SDS, 2mM EDTA). SSC is 0.15M sodium chloride/0.15M sodium citrate, pH7; SDS is sodium dodecyl sulphate; and EDTA is ethylenediaminetetracetic acid. After hybridization, the membrane upon which the DNA is transferred is washed at 2 x SSC at room temperature and then at 0.1 x SSC/0.1 x SDS at temperatures up to 68°C.

There are other conditions, reagents, and so forth which can be used, and would result in a similar degree of stringency. The skilled artisan will be familiar with such conditions, and thus they are not given here. It will be understood, however, that the skilled artisan will be able to manipulate the conditions in a manner to permit the clear identification of homologs and alleles of the SOC/CRAC nucleic acids of the invention. The skilled artisan also is familiar with the methodology for screening cells and libraries for expression of such

molecules which then are routinely isolated, followed by isolation of the pertinent nucleic acid molecule and sequencing.

In general homologs and alleles typically will share at least 40% nucleotide identity and/or at least 50% amino acid identity to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and/or SEQ ID NO:31, and SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and/or SEQ ID NO:32, respectively. In some instances sequences will share at least 50% nucleotide identity and/or at least 65% amino acid identity and in still other instances sequences will share at least 60% nucleotide identity and/or at least 75% amino acid identity. The homology can be calculated using various, publicly available software tools developed by NCBI (Bethesda, Maryland) that can be obtained through the internet (<ftp://ncbi.nlm.nih.gov/pub/>). Exemplary tools include the BLAST system available at <http://www.ncbi.nlm.nih.gov>. Pairwise and ClustalW alignments (BLOSUM30 matrix setting) as well as Kyte-Doolittle hydropathic analysis can be obtained using the MacVector sequence analysis software (Oxford Molecular Group). Watson-Crick complements of the foregoing nucleic acids also are embraced by the invention.

In screening for SOC/CRAC related genes, such as homologs and alleles of SOC-2/CRAC-1 and/or SOC-3/CRAC-2, a Southern blot may be performed using the foregoing conditions, together with a radioactive probe. After washing the membrane to which the DNA is finally transferred, the membrane can be placed against X-ray film or a phosphorimager plate to detect the radioactive signal.

Given that the expression of the SOC/CRAC gene is prominent in certain human tissues (e.g., SOC-2/CRAC-1: lymphoid tissue/heart, SOC-3/CRAC-2: kidney/colon, SOC-4/CRAC-3: prostate), and given the teachings herein of partial human SOC/CRAC cDNA clones, full-length and other mammalian sequences corresponding to the human SOC/CRAC partial nucleic acid sequences can be isolated from, for example, a cDNA library prepared from one or more of the tissues in which SOC-2/CRAC-1 expression is prominent, SOC-3/CRAC-2 is prominent, and/or SOC-4/CRAC-3 expression is prominent, using standard colony hybridization techniques.

The invention also includes degenerate nucleic acids which include alternative codons to those present in the native materials. For example, serine residues are encoded by the codons TCA, AGT, TCC, TCG, TCT and AGC. Each of the six codons is equivalent for the purposes of encoding a serine residue. Thus, it will be apparent to one of ordinary skill in the

art that any of the serine-encoding nucleotide triplets may be employed to direct the protein synthesis apparatus, *in vitro* or *in vivo*, to incorporate a serine residue into an elongating SOC/CRAC polypeptide. Similarly, nucleotide sequence triplets which encode other amino acid residues include, but are not limited to: CCA, CCC, CCG and CCT (proline codons); CGA, CGC, CGG, CGT, AGA and AGG (arginine codons); ACA, ACC, ACG and ACT (threonine codons); AAC and AAT (asparagine codons); and ATA, ATC and ATT (isoleucine codons). Other amino acid residues may be encoded similarly by multiple nucleotide sequences. Thus, the invention embraces degenerate nucleic acids that differ from the biologically isolated nucleic acids in codon sequence due to the degeneracy of the genetic code.

The invention also provides isolated unique fragments of an isolated nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31. A unique fragment is one that is a 'signature' for the larger nucleic acid. For example, the unique fragment is long enough to assure that its precise sequence is not found in molecules within the human genome outside of the SOC/CRAC nucleic acids defined above (and human alleles). Those of ordinary skill in the art may apply no more than routine procedures to determine if a fragment is unique within the human genome.

Unique fragments, however, exclude fragments completely composed of the nucleotide sequences of any of GenBank accession numbers and SEQ ID NOs listed in Table I (SEQ ID NO:9, AB001535, AI226731, H18835, AA419592, AA261842, AA419407, AI098310, AA592910, D86107, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, AC005538, AA654650, AA370110, AA313170, AA493512, AI670079, AI671853, AC005538, AA654650, AA370110, AA313170, AA493512, AI670079, AI671853), or other previously published sequences as of the filing date of this application.

A fragment which is completely composed of the sequence described in the foregoing GenBank deposits and SEQ ID NO:9, is one which does not include any of the nucleotides unique to the sequences of the invention. Thus, a unique fragment must contain a nucleotide sequence other than the exact sequence of those in GenBank or fragments thereof. The difference may be an addition, deletion or substitution with respect to the GenBank sequence or it may be a sequence wholly separate from the GenBank sequence.

-17-

Unique fragments can be used as probes in Southern and Northern blot assays to identify such nucleic acids, or can be used in amplification assays such as those employing PCR. As known to those skilled in the art, large probes such as 200, 250, 300 or more nucleotides are preferred for certain uses such as Southern and Northern blots, while smaller fragments will be preferred for uses such as PCR. Unique fragments also can be used to produce fusion proteins for generating antibodies or determining binding of the polypeptide fragments, as demonstrated in the Examples, or for generating immunoassay components. Likewise, unique fragments can be employed to produce nonfused fragments of the SOC/CRAC polypeptides, useful, for example, in the preparation of antibodies, immunoassays or therapeutic applications. Unique fragments further can be used as antisense molecules to inhibit the expression of SOC/CRAC nucleic acids and polypeptides, respectively.

As will be recognized by those skilled in the art, the size of the unique fragment will depend upon its conservancy in the genetic code. Thus, some regions of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, and complements thereof, will require longer segments to be unique while others will require only short segments, typically between 12 and 32 nucleotides long (e.g. 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 and 32 bases) or more, up to the entire length of the disclosed sequence. As mentioned above, this disclosure intends to embrace each and every fragment of each sequence, beginning at the first nucleotide, the second nucleotide and so on, up to 8 nucleotides short of the end, and ending anywhere from nucleotide number 8, 9, 10 and so on for each sequence, up to the very last nucleotide, (provided the sequence is unique as described above). Virtually any segment of the region of SEQ ID NO:1 beginning at nucleotide 1 and ending at nucleotide 1212, or SEQ ID NO:3 beginning at nucleotide 1 and ending at nucleotide 739, or SEQ ID NO:5 beginning at nucleotide 1 and ending at nucleotide 1579, or SEQ ID NO:7 beginning at nucleotide 1 and ending at nucleotide 3532, or SEQ ID NO:23 beginning at nucleotide 1 and ending at nucleotide 5117, SEQ ID NO:25 beginning at nucleotide 1 and ending at nucleotide 2180, SEQ ID NO:27 beginning at nucleotide 1 and ending at nucleotide 7419, or SEQ ID NO:29 beginning at nucleotide 1 and ending at nucleotide 4061, or SEQ ID NO:31 beginning at nucleotide 1 and ending at nucleotide 4646, or complements thereof, that is 20 or more nucleotides in length will be unique. Those skilled in the art are well versed in methods for selecting such sequences, typically on the basis of the ability of the unique

fragment to selectively distinguish the sequence of interest from other sequences in the human genome of the fragment to those on known databases typically is all that is necessary, although *in vitro* confirmatory hybridization and sequencing analysis may be performed.

As mentioned above, the invention embraces antisense oligonucleotides that selectively bind to a nucleic acid molecule encoding a SOC/CRAC polypeptide, to decrease SOC/CRAC calcium channel activity. When using antisense preparations of the invention, slow intravenous administration is preferred.

As used herein, the term "antisense oligonucleotide" or "antisense" describes an oligonucleotide that is an oligoribonucleotide, oligodeoxyribonucleotide, modified oligoribonucleotide, or modified oligodeoxyribonucleotide which hybridizes under physiological conditions to DNA comprising a particular gene or to an mRNA transcript of that gene and, thereby, inhibits the transcription of that gene and/or the translation of that mRNA. The antisense molecules are designed so as to interfere with transcription or translation of a target gene upon hybridization with the target gene or transcript. Those skilled in the art will recognize that the exact length of the antisense oligonucleotide and its degree of complementarity with its target will depend upon the specific target selected, including the sequence of the target and the particular bases which comprise that sequence. It is preferred that the antisense oligonucleotide be constructed and arranged so as to bind selectively with the target under physiological conditions, i.e., to hybridize substantially more to the target sequence than to any other sequence in the target cell under physiological conditions. Based upon SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, or upon allelic or homologous genomic and/or cDNA sequences, one of skill in the art can easily choose and synthesize any of a number of appropriate antisense molecules for use in accordance with the present invention. In order to be sufficiently selective and potent for inhibition, such antisense oligonucleotides should comprise at least 10 and, more preferably, at least 15 consecutive bases which are complementary to the target, although in certain cases modified oligonucleotides as short as 7 bases in length have been used successfully as antisense oligonucleotides (Wagner et al., *Nat. Med.* 1(11):1116-1118, 1995). Most preferably, the antisense oligonucleotides comprise a complementary sequence of 20-30 bases. Although oligonucleotides may be chosen which are antisense to any region of the gene or mRNA transcripts, in preferred embodiments the antisense oligonucleotides correspond to N-terminal or 5' upstream sites such as translation initiation, transcription initiation or promoter sites. In

addition, 3'-untranslated regions may be targeted by antisense oligonucleotides. Targeting to mRNA splicing sites has also been used in the art but may be less preferred if alternative mRNA splicing occurs. In addition, the antisense is targeted, preferably, to sites in which mRNA secondary structure is not expected (see, e.g., Sainio et al., *Cell Mol. Neurobiol.* 14(5):439-457, 1994) and at which proteins are not expected to bind. Finally, although, SEQ ID No:1 discloses a cDNA sequence, one of ordinary skill in the art may easily derive the genomic DNA corresponding to this sequence. Thus, the present invention also provides for antisense oligonucleotides which are complementary to the genomic DNA corresponding to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31. Similarly, antisense to allelic or homologous SOC/CRAC cDNAs and genomic DNAs are enabled without undue experimentation.

In one set of embodiments, the antisense oligonucleotides of the invention may be composed of "natural" deoxyribonucleotides, ribonucleotides, or any combination thereof. That is, the 5' end of one native nucleotide and the 3' end of another native nucleotide may be covalently linked, as in natural systems, via a phosphodiester internucleoside linkage. These oligonucleotides may be prepared by art recognized methods which may be carried out manually or by an automated synthesizer. They also may be produced recombinantly by vectors.

In preferred embodiments, however, the antisense oligonucleotides of the invention also may include "modified" oligonucleotides. That is, the oligonucleotides may be modified in a number of ways which do not prevent them from hybridizing to their target but which enhance their stability or targeting or which otherwise enhance their therapeutic effectiveness.

The term "modified oligonucleotide" as used herein describes an oligonucleotide in which (1) at least two of its nucleotides are covalently linked via a synthetic internucleoside linkage (i.e., a linkage other than a phosphodiester linkage between the 5' end of one nucleotide and the 3' end of another nucleotide) and/or (2) a chemical group not normally associated with nucleic acids has been covalently attached to the oligonucleotide. Preferred synthetic internucleoside linkages are phosphorothioates, alkylphosphonates, phosphorodithioates, phosphate esters, alkylphosphonothioates, phosphoramidates, carbamates, carbonates, phosphate triesters, acetamidates, carboxymethyl esters and peptides.

The term "modified oligonucleotide" also encompasses oligonucleotides with a covalently modified base and/or sugar. For example, modified oligonucleotides include

oligonucleotides having backbone sugars which are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 3' position and other than a phosphate group at the 5' position. Thus modified oligonucleotides may include a 2'-O-alkylated ribose group. In addition, modified oligonucleotides may include sugars such as arabinose instead of ribose. The present invention, thus, contemplates pharmaceutical preparations containing modified antisense molecules that are complementary to and hybridizable with, under physiological conditions, nucleic acids encoding SOC/CRAC polypeptides, together with pharmaceutically acceptable carriers. Antisense oligonucleotides may be administered as part of a pharmaceutical composition. Such a pharmaceutical composition may include the antisense oligonucleotides in combination with any standard physiologically and/or pharmaceutically acceptable carriers which are known in the art. The compositions should be sterile and contain a therapeutically effective amount of the antisense oligonucleotides in a unit of weight or volume suitable for administration to a patient. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients. The term "physiologically acceptable" refers to a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism. The characteristics of the carrier will depend on the route of administration. Physiologically and pharmaceutically acceptable carriers include diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials which are well known in the art.

The invention also involves expression vectors coding for SOC/CRAC proteins and fragments and variants thereof and host cells containing those expression vectors. Virtually any cells, prokaryotic or eukaryotic, which can be transformed with heterologous DNA or RNA and which can be grown or maintained in culture, may be used in the practice of the invention. Examples include bacterial cells such as E.coli and eukaryotic cells such as mouse, hamster, pig, goat, primate, yeast, xenopous, etc. They may be of a wide variety of tissue types, including mast cells, fibroblasts, oocytes and lymphocytes, and they may be primary cells or cell lines. Specific examples include CHO cells and COS cells. Cell-free transcription systems also may be used in lieu of cells.

As used herein, a "vector" may be any of a number of nucleic acids into which a desired sequence may be inserted by restriction and ligation for transport between different genetic environments or for expression in a host cell. Vectors are typically composed of DNA although RNA vectors are also available. Vectors include, but are not limited to,

plasmids, phagemids and virus genomes. A cloning vector is one which is able to replicate in a host cell, and which is further characterized by one or more endonuclease restriction sites at which the vector may be cut in a determinable fashion and into which a desired DNA sequence may be ligated such that the new recombinant vector retains its ability to replicate in the host cell. In the case of plasmids, replication of the desired sequence may occur many times as the plasmid increases in copy number within the host bacterium or just a single time per host before the host reproduces by mitosis. In the case of phage, replication may occur actively during a lytic phase or passively during a lysogenic phase. An expression vector is one into which a desired DNA sequence may be inserted by restriction and ligation such that it is operably joined to regulatory sequences and may be expressed as an RNA transcript. Vectors may further contain one or more marker sequences suitable for use in the identification of cells which have or have not been transformed or transfected with the vector. Markers include, for example, genes encoding proteins which increase or decrease either resistance or sensitivity to antibiotics or other compounds, genes which encode enzymes whose activities are detectable by standard assays known in the art (e.g., β -galactosidase or alkaline phosphatase), and genes which visibly affect the phenotype of transformed or transfected cells, hosts, colonies or plaques (e.g., green fluorescent protein). Preferred vectors are those capable of autonomous replication and expression of the structural gene products present in the DNA segments to which they are operably joined.

As used herein, a coding sequence and regulatory sequences are said to be "operably" joined when they are covalently linked in such a way as to place the expression or transcription of the coding sequence under the influence or control of the regulatory sequences. If it is desired that the coding sequences be translated into a functional protein, two DNA sequences are said to be operably joined if induction of a promoter in the 5' regulatory sequences results in the transcription of the coding sequence and if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter region to direct the transcription of the coding sequences, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. Thus, a promoter region would be operably joined to a coding sequence if the promoter region were capable of effecting transcription of that DNA sequence such that the resulting transcript might be translated into the desired protein or polypeptide.

The precise nature of the regulatory sequences needed for gene expression may vary between species or cell types, but shall in general include, as necessary, 5' non-transcribed

and 5' non-translated sequences involved with the initiation of transcription and translation respectively, such as a TATA box, capping sequence, CAAT sequence, and the like. Especially, such 5' non-transcribed regulatory sequences will include a promoter region which includes a promoter sequence for transcriptional control of the operably joined gene. Regulatory sequences may also include enhancer sequences or upstream activator sequences as desired. The vectors of the invention may optionally include 5' leader or signal sequences. The choice and design of an appropriate vector is within the ability and discretion of one of ordinary skill in the art.

According to yet another aspect of the invention, isolated SOC/CRAC polypeptides are provided. Preferably, the isolated SOC/CRAC polypeptides are encoded by the isolated SOC/CRAC nucleic acid molecules disclosed herein. More preferably, the isolated SOC/CRAC polypeptides of the invention are encoded by the nucleic acid molecules having SEQ ID Nos. 1, 3, 5, 7, 23, 25, 27, 29, and 31. In yet other embodiments, the isolated SOC/CRAC polypeptides of the invention have an amino acid sequence selected from the group consisting of SEQ ID Nos. 2, 4, 6, 8, 24, 26, 28, 30 and 32. Preferably, the isolated SOC/CRAC polypeptides are of sufficient length to represent a sequence unique within the human genome. Thus, the preferred embodiments include a sequence of contiguous amino acids which is not identical to a prior art sequence as represented by the sequence group consisting of the contiguous amino acids identified in Table II (SEQ ID NO:10, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19 and GenBank Acc. Nos. AB001535, AA592910, D86107, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, NP003298, CAB00861, NP002411, CAA92726, CAB05572).

In certain embodiments, the isolated SOC/CRAC polypeptides are immunogenic and can be used to generate binding polypeptides (e.g., antibodies) for use in diagnostic and therapeutic applications. Such binding polypeptides also are useful for detecting the presence, absence, and/or amounts of a SOC/CRAC nucleic acid or polypeptide in a sample such as a biological fluid or biopsy sample. Preferably, the SOC/CRAC polypeptides that are useful for generating binding polypeptides are unique polypeptides and, therefore, binding of the antibody to a SOC/CRAC polypeptide in a sample is selective for the SOC/CRAC polypeptide.

Expression vectors containing all the necessary elements for expression are commercially available and known to those skilled in the art. See, e.g., Sambrook et al.,

Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989. Cells are genetically engineered by the introduction into the cells of heterologous DNA (RNA) encoding a SOC/CRAC polypeptide or fragment or variant thereof. The heterologous DNA (RNA) is placed under operable control of transcriptional elements to permit the expression of the heterologous DNA in the host cell.

Preferred systems for mRNA expression in mammalian cells are those such as pRc/CMV (available from Invitrogen, Carlsbad, CA) that contain a selectable marker such as a gene that confers G418 resistance (which facilitates the selection of stably transfected cell lines) and the human cytomegalovirus (CMV) enhancer-promoter sequences. Additionally, suitable for expression in primate or canine cell lines is the pCEP4 vector (Invitrogen, Carlsbad, CA), which contains an Epstein Barr virus (EBV) origin of replication, facilitating the maintenance of plasmid as a multicopy extrachromosomal element. Another expression vector is the pEF-BOS plasmid containing the promoter of polypeptide Elongation Factor 1 α , which stimulates efficiently transcription *in vitro*. The plasmid is described by Mishizuma and Nagata (*Nuc. Acids Res.* 18:5322, 1990), and its use in transfection experiments is disclosed by, for example, Demoulin (*Mol. Cell. Biol.* 16:4710-4716, 1996). Still another preferred expression vector is an adenovirus, described by Stratford-Perricaudet, which is defective for E1 and E3 proteins (*J. Clin. Invest.* 90:626-630, 1992). The use of the adenovirus as an Adeno.P1A recombinant is disclosed by Warnier et al., in intradermal injection in mice for immunization against P1A (*Int. J. Cancer*, 67:303-310, 1996).

The invention also embraces so-called expression kits, which allow the artisan to prepare a desired expression vector or vectors. Such expression kits include at least separate portions of each of the previously discussed coding sequences. Other components may be added, as desired, as long as the previously mentioned sequences, which are required, are included.

It will also be recognized that the invention embraces the use of the above described, SOC/CRAC cDNA sequence containing expression vectors, to transfect host cells and cell lines, by these prokaryotic (e.g., *E. coli*), or eukaryotic (e.g., CHO cells, COS cells, yeast expression systems and recombinant baculovirus expression in insect cells). Especially useful are mammalian cells such as mouse, hamster, pig, goat, primate, etc. They may be of a wide variety of tissue types, and include primary cells and cell lines. Specific examples include dendritic cells, U293 cells, peripheral blood leukocytes, bone marrow stem cells and embryonic stem cells. The invention also permits the construction of SOC/CRAC gene

"knock-outs" in cells and in animals, providing materials for studying certain aspects of SOC/CRAC calcium channel activity.

The invention also provides isolated polypeptides (including whole proteins and partial proteins), encoded by the foregoing SOC/CRAC nucleic acids, and include the polypeptides of SEQ ID NO:2, 4, 6, 8, 24, 26, 28, 30, 32, and unique fragments thereof. Such polypeptides are useful, for example, to regulate calcium transport-mediated cell growth, differentiation and proliferation, to generate antibodies, as components of immunoassays, etc. Polypeptides can be isolated from biological samples including tissue or cell homogenates, and can also be expressed recombinantly in a variety of prokaryotic and eukaryotic expression systems by constructing an expression vector appropriate to the expression system, introducing the expression vector into the expression system, and isolating the recombinantly expressed protein. Short polypeptides, including antigenic peptides (such as are presented by MHC molecules on the surface of a cell for immune recognition) also can be synthesized chemically using well-established methods of peptide synthesis.

A unique fragment of a SOC/CRAC polypeptide, in general, has the features and characteristics of unique fragments as discussed above in connection with nucleic acids. As will be recognized by those skilled in the art, the size of the unique fragment will depend upon factors such as whether the fragment constitutes a portion of a conserved protein domain. Thus, some regions of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and/or SEQ ID NO:32, will require longer segments to be unique while others will require only short segments, typically between 5 and 12 amino acids (e.g. 5, 6, 7, 8, 9, 10, 11 and 12 amino acids long or more, including each integer up to the full length, >1,000 amino acids long). Virtually any segment of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and/or SEQ ID NO:32, excluding the ones that share identity with it (the polypeptides identified in Table II - SEQ ID NO:10, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, and GenBank Acc. Nos. AB001535, AA592910, D86107, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, NP003298, CAB00861, NP002411, CAA92726, CAB05572) that is 9 or more amino acids in length will be unique.

Unique fragments of a polypeptide preferably are those fragments which retain a distinct functional capability of the polypeptide. Functional capabilities which can be retained in a unique fragment of a polypeptide include Ca^{2+} fluxing, high selectivity, a unitary

conductance below the detection level of the patch clamp method, and/or and are subject to inhibition by high intracellular calcium levels.

One important aspect of a unique fragment is its ability to act as a signature for identifying the polypeptide. Optionally, another aspect of a unique fragment is its ability to provide an immune response in an animal. Those skilled in the art are well versed in methods for selecting unique amino acid sequences, typically on the basis of the ability of the unique fragment to selectively distinguish the sequence of interest from non-family members. A comparison of the sequence of the fragment to those on known databases typically is all that is necessary.

The invention embraces variants of the SOC/CRAC polypeptides described above. As used herein, a "variant" of a SOC/CRAC polypeptide is a polypeptide which contains one or more modifications to the primary amino acid sequence of a SOC/CRAC polypeptide. Modifications which create a SOC/CRAC polypeptide variant are typically made to the nucleic acid which encodes the SOC/CRAC polypeptide, and can include deletions, point mutations, truncations, amino acid substitutions and addition of amino acids or non-amino acid moieties to:

- 1) reduce or eliminate a calcium channel activity of a SOC/CRAC polypeptide;
- 2) enhance a property of a SOC/CRAC polypeptide, such as protein stability in an expression system or the stability of protein-protein binding;
- 3) provide a novel activity or property to a SOC/CRAC polypeptide, such as addition of an antigenic epitope or addition of a detectable moiety; or
- 4) to provide equivalent or better binding to a SOC/CRAC polypeptide receptor or other molecule.

Alternatively, modifications can be made directly to the polypeptide, such as by cleavage, addition of a linker molecule, addition of a detectable moiety, such as biotin, addition of a fatty acid, and the like. Modifications also embrace fusion proteins comprising all or part of the SOC/CRAC amino acid sequence. One of skill in the art will be familiar with methods for predicting the effect on protein conformation of a change in protein sequence, and can thus "design" a variant SOC/CRAC polypeptide according to known methods. One example of such a method is described by Dahiyat and Mayo in *Science* 278:82-87, 1997, whereby proteins can be designed *de novo*. The method can be applied to a known protein to vary only a portion of the polypeptide sequence. By applying the computational methods of Dahiyat and Mayo, specific variants of a SOC/CRAC calcium channel polypeptide can be proposed and tested to determine whether the variant retains a desired conformation.

5 Variants can include SOC/CRAC polypeptides which are modified specifically to alter a feature of the polypeptide unrelated to its physiological activity. For example, cysteine residues can be substituted or deleted to prevent unwanted disulfide linkages. Similarly, certain amino acids can be changed to enhance expression of a SOC/CRAC polypeptide by eliminating proteolysis by proteases in an expression system (e.g., dibasic amino acid residues in yeast expression systems in which KEX2 protease activity is present).

10 Mutations of a nucleic acid which encodes a SOC/CRAC polypeptide preferably preserve the amino acid reading frame of the coding sequence and, preferably, do not create regions in the nucleic acid which are likely to hybridize to form secondary structures, such as hairpins or loops, which can be deleterious to expression of the variant polypeptide.

15 Mutations can be made by selecting an amino acid substitution, or by random mutagenesis of a selected site in a nucleic acid which encodes the polypeptide. Variant polypeptides are then expressed and tested for one or more activities to determine which mutation provides a variant polypeptide with the desired properties. Further mutations can be made to variants (or to non-variant SOC/CRAC polypeptides) which are silent as to the amino acid sequence of the polypeptide, but which provide preferred codons for translation in a particular host. The preferred codons for translation of a nucleic acid in, e.g., *E. coli*, are well known to those of ordinary skill in the art. Still other mutations can be made to the noncoding sequences of a SOC/CRAC gene or cDNA clone to enhance expression of the polypeptide.

20 The skilled artisan will realize that conservative amino acid substitutions may be made in SOC/CRAC polypeptides to provide functionally equivalent variants of the foregoing polypeptides, i.e., the variants retain the functional capabilities of the SOC/CRAC polypeptides. As used herein, a "conservative amino acid substitution" refers to an amino acid substitution which does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Variants can be prepared according to methods for altering polypeptide sequence known to one of ordinary skill in the art such as are found in references which compile such methods, e.g. *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. Exemplary functionally equivalent variants of the SOC/CRAC polypeptides include conservative amino acid substitutions of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and/or SEQ ID NO:32. Conservative substitutions of amino acids

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include substitutions made amongst amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q, N; and (g) E, D.

Thus functionally equivalent variants of SOC/CRAC polypeptides, i.e., variants of SOC/CRAC polypeptides which retain the function of the natural SOC/CRAC polypeptides, are contemplated by the invention. Conservative amino-acid substitutions in the amino acid sequence of SOC/CRAC polypeptides to produce functionally equivalent variants of SOC/CRAC polypeptides typically are made by alteration of a nucleic acid encoding SOC/CRAC polypeptides (e.g., SEQ ID NOs:1, 3, 5, 7, 23, 25, 27, 29, 31). Such substitutions can be made by a variety of methods known to one of ordinary skill in the art. For example, amino acid substitutions may be made by PCR-directed mutation, site-directed mutagenesis according to the method of Kunkel (Kunkel, *Proc. Nat. Acad. Sci. U.S.A.* 82: 488-492, 1985), or by chemical synthesis of a gene encoding a SOC/CRAC polypeptide. The activity of functionally equivalent fragments of SOC/CRAC polypeptides can be tested by cloning the gene encoding the altered SOC/CRAC polypeptide into a bacterial or mammalian expression vector, introducing the vector into an appropriate host cell, expressing the altered SOC/CRAC polypeptide, and testing for a functional capability of the SOC/CRAC polypeptides as disclosed herein (e.g., SOC/CRAC calcium channel activity).

The invention as described herein has a number of uses, some of which are described elsewhere herein. First, the invention permits isolation of SOC/CRAC polypeptides, including the isolation of the complete SOC/CRAC polypeptide. A variety of methodologies well-known to the skilled practitioner can be utilized to obtain isolated SOC/CRAC molecules. The polypeptide may be purified from cells which naturally produce the polypeptide by chromatographic means or immunological recognition. Alternatively, an expression vector may be introduced into cells to cause production of the polypeptide. In another method, mRNA transcripts may be microinjected or otherwise introduced into cells to cause production of the encoded polypeptide. Translation of SOC/CRAC mRNA in cell-free extracts such as the reticulocyte lysate system also may be used to produce SOC/CRAC polypeptides. Those skilled in the art also can readily follow known methods for isolating SOC/CRAC polypeptides. These include, but are not limited to, immunochromatography, HPLC, size-exclusion chromatography, ion-exchange chromatography and immune-affinity chromatography.

The invention also provides, in certain embodiments, "dominant negative" polypeptides derived from SOC/CRAC polypeptides. A dominant negative polypeptide is an

inactive variant of a protein, which, by interacting with the cellular machinery, displaces an active protein from its interaction with the cellular machinery or competes with the active protein, thereby reducing the effect of the active protein. For example, a dominant negative receptor which binds a ligand but does not transmit a signal in response to binding of the ligand can reduce the biological effect of expression of the ligand. Likewise, a dominant negative inactive SOC/CRAC calcium channel which interacts normally with the cell membrane but which does not mediate calcium transport can reduce calcium transport in a cell. Similarly, a dominant negative transcription factor which binds to a promoter site in the control region of a gene but does not increase gene transcription can reduce the effect of a normal transcription factor by occupying promoter binding sites without increasing transcription.

The end result of the expression of a dominant negative polypeptide in a cell is a reduction in function of active proteins. One of ordinary skill in the art can assess the potential for a dominant negative variant of a protein, and using standard mutagenesis techniques to create one or more dominant negative variant polypeptides. See, e.g., U.S. Patent No. 5,580,723 and Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press. The skilled artisan then can test the population of mutagenized polypeptides for diminution in a selected and/or for retention of such an activity. Other similar methods for creating and testing dominant negative variants of a protein will be apparent to one of ordinary skill in the art.

According to another aspect, the invention provides a method for isolating a SOC/CRAC molecule having SOC/CRAC calcium channel activity. The method involves contacting a binding molecule that is a SOC/CRAC nucleic acid or a SOC/CRAC binding polypeptide with a sample containing one or more SOC/CRAC molecules under conditions that allow such binding (see earlier discussion) to form a complex, detecting the presence of the complex, isolating the SOC/CRAC molecule from the complex, and determining whether the isolated SOC/CRAC molecule has SOC/CRAC calcium channel activity. Thus, the invention is useful for identifying and isolating full length complementary (cDNA) or genomic nucleic acids encoding SOC/CRAC polypeptides having SOC/CRAC calcium channel activity. Identification and isolation of such nucleic acids and polypeptides may be accomplished by hybridizing/binding, under appropriate conditions well known in the art, libraries and/or restriction enzyme-digested human nucleic acids, with a labeled SOC/CRAC molecular probe. As used herein, a "label" includes molecules that are incorporated into, for

example, a SOC/CRAC molecule (nucleic acid or peptide), that can be directly or indirectly detected. A wide variety of detectable labels are well known in the art that can be used, and include labels that provide direct detection (e.g., radioactivity, luminescence, optical or electron density, etc), or indirect detection (e.g., epitope tag such as the FLAG epitope, enzyme tag such as horseradish peroxidase, etc.). The label may be bound to a SOC/CRAC binding partner, or incorporated into the structure of the binding partner.

A variety of methods may be used to detect the label, depending on the nature of the label and other assay components. For example, the label may be detected while bound to the solid substrate or subsequent to separation from the solid substrate. Labels may be directly detected through optical or electron density, radioactive emissions, nonradioactive energy transfers, etc. or indirectly detected with antibody conjugates, streptavidin-biotin conjugates, etc. Methods for detecting the labels are well known in the art. Once a library clone or hybridizing fragment is identified in the hybridization/binding reaction, it can be further isolated by employing standard isolation/cloning techniques known to those of skill in the art. See, generally, Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*, 2nd Edition, Cold Spring Harbor Laboratory Press. In addition, nucleic acid amplification techniques well known in the art, may also be used to locate splice variants of calcium channel (or calcium channel subunits) with SOC/CRAC calcium channel activity. Size and sequence determinations of the amplification products can reveal splice variants.

The foregoing isolated nucleic acids and polypeptides may then be compared to the nucleic acids and polypeptides of the present invention in order to identify homogeneity or divergence of the sequences, and be further characterized functionally to determine whether they belong to a family of molecules with SOC/CRAC calcium channel activity (for methodology see under the Examples section).

The isolation of the SOC/CRAC cDNA and/or partial sequences thereof also makes it possible for the artisan to diagnose a disorder characterized by an aberrant expression of SOC/CRAC. These methods involve determining expression of the SOC/CRAC gene, and/or SOC/CRAC polypeptides derived therefrom. In the former situation, such determinations can be carried out via any standard nucleic acid determination assay, including the polymerase chain reaction, or assaying with labeled hybridization probes as exemplified below. In the latter situation, such determination can be carried out via any standard immunological assay using, for example, antibodies which bind to the SOC/CRAC protein.

The invention also embraces isolated peptide binding agents which, for example, can be antibodies or fragments of antibodies ("binding polypeptides"), having the ability to selectively bind to SOC/CRAC polypeptides. Antibodies include polyclonal and monoclonal antibodies, prepared according to conventional methodology. In certain embodiments, the invention excludes binding agents (e.g., antibodies) that bind to the polypeptides encoded by the nucleic acids of SEQ ID NOs: 10, 12, 13, 14, 15, 17, and 19.

Significantly, as is well-known in the art, only a small portion of an antibody molecule, the paratope, is involved in the binding of the antibody to its epitope (see, in general, Clark, W.R. (1986) The Experimental Foundations of Modern Immunology Wiley & Sons, Inc., New York; Roitt, I. (1991) Essential Immunology, 7th Ed., Blackwell Scientific Publications, Oxford). The pFc' and Fc regions, for example, are effectors of the complement cascade but are not involved in antigen binding. An antibody from which the pFc' region has been enzymatically cleaved, or which has been produced without the pFc' region, designated an F(ab')₂ fragment, retains both of the antigen binding sites of an intact antibody. Similarly, an antibody from which the Fc region has been enzymatically cleaved, or which has been produced without the Fc region, designated an Fab fragment, retains one of the antigen binding sites of an intact antibody molecule. Proceeding further, Fab fragments consist of a covalently bound antibody light chain and a portion of the antibody heavy chain denoted Fd. The Fd fragments are the major determinant of antibody specificity (a single Fd fragment may be associated with up to ten different light chains without altering antibody specificity) and Fd fragments retain epitope-binding ability in isolation.

Within the antigen-binding portion of an antibody, as is well-known in the art, there are complementarity determining regions (CDRs), which directly interact with the epitope of the antigen, and framework regions (FRs), which maintain the tertiary structure of the paratope (see, in general, Clark, 1986; Roitt, 1991). In both the heavy chain Fd fragment and the light chain of IgG immunoglobulins, there are four framework regions (FR1 through FR4) separated respectively by three complementarity determining regions (CDR1 through CDR3). The CDRs, and in particular the CDR3 regions, and more particularly the heavy chain CDR3, are largely responsible for antibody specificity.

It is now well-established in the art that the non-CDR regions of a mammalian antibody may be replaced with similar regions of conspecific or heterospecific antibodies while retaining the epitopic specificity of the original antibody. This is most clearly manifested in the development and use of "humanized" antibodies in which non-human CDRs

are covalently joined to human FR and/or Fc/pFc' regions to produce a functional antibody. Thus, for example, PCT International Publication Number WO 92/04381 teaches the production and use of humanized murine RSV antibodies in which at least a portion of the murine FR regions have been replaced by FR regions of human origin. Such antibodies, including fragments of intact antibodies with antigen-binding ability, are often referred to as "chimeric" antibodies.

Thus, as will be apparent to one of ordinary skill in the art, the present invention also provides for F(ab')₂, Fab, Fv and Fd fragments; chimeric antibodies in which the Fc and/or FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric F(ab')₂ fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric Fab fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; and chimeric Fd fragment antibodies in which the FR and/or CDR1 and/or CDR2 regions have been replaced by homologous human or non-human sequences. The present invention also includes so-called single chain antibodies.

Thus, the invention involves binding polypeptides of numerous size and type that bind selectively to SOC/CRAC polypeptides, and complexes containing SOC/CRAC polypeptides. These binding polypeptides also may be derived also from sources other than antibody technology. For example, such polypeptide binding agents can be provided by degenerate peptide libraries which can be readily prepared in solution, in immobilized form, as bacterial flagella peptide display libraries or as phage display libraries. Combinatorial libraries also can be synthesized of peptides containing one or more amino acids. Libraries further can be synthesized of peptides and non-peptide synthetic moieties.

Phage display can be particularly effective in identifying binding peptides useful according to the invention. Briefly, one prepares a phage library (using e.g. m13, fd, or lambda phage), displaying inserts from 4 to about 80 amino acid residues using conventional procedures. The inserts may represent, for example, a completely degenerate or biased array. One then can select phage-bearing inserts which bind to the SOC/CRAC polypeptide or a complex containing a SOC/CRAC polypeptide. This process can be repeated through several cycles of reselection of phage that bind to the SOC/CRAC polypeptide or complex. Repeated rounds lead to enrichment of phage bearing particular sequences. DNA sequence analysis can be conducted to identify the sequences of the expressed polypeptides. The minimal linear

portion of the sequence that binds to the SOC/CRAC polypeptide or complex can be determined. One can repeat the procedure using a biased library containing inserts containing part or all of the minimal linear portion plus one or more additional degenerate residues upstream or downstream thereof. Yeast two-hybrid screening methods also may be used to
5 identify polypeptides that bind to the SOC/CRAC polypeptides. Thus, the SOC/CRAC polypeptides of the invention, or a fragment thereof, or complexes of SOC/CRAC can be used to screen peptide libraries, including phage display libraries, to identify and select peptide binding polypeptides that selectively bind to the SOC/CRAC polypeptides of the invention. Such molecules can be used, as described, for screening assays, for purification protocols, for
10 interfering directly with the functioning of SOC/CRAC and for other purposes that will be apparent to those of ordinary skill in the art.

A SOC/CRAC polypeptide, or a fragment thereof, also can be used to isolate naturally occurring, polypeptide binding partners which may associate with the SOC/CRAC polypeptide in the membrane of a cell. Isolation of binding partners may be performed
15 according to well-known methods. For example, isolated SOC/CRAC polypeptides can be attached to a substrate, and then a solution suspected of containing an SOC/CRAC binding partner may be applied to the substrate. If the binding partner for SOC/CRAC polypeptides is present in the solution, then it will bind to the substrate-bound SOC/CRAC polypeptide. The binding partner then may be isolated. Other proteins which are binding partners for
20 SOC/CRAC, may be isolated by similar methods without undue experimentation.

The invention also provides novel kits which could be used to measure the levels of the nucleic acids of the invention, expression products of the invention or anti-SOC/CRAC antibodies. In the case of nucleic acid detection, pairs of primers for amplifying SOC/CRAC nucleic acids can be included. The preferred kits would include controls such as known
25 amounts of nucleic acid probes, SOC/CRAC epitopes (such as SOC/CRAC expression products) or anti-SOC/CRAC antibodies, as well as instructions or other printed material. In certain embodiments the printed material can characterize risk of developing a disorder that is characterized by aberrant SOC/CRAC polypeptide expression based upon the outcome of the assay. The reagents may be packaged in containers and/or coated on wells in predetermined
30 amounts, and the kits may include standard materials such as labeled immunological reagents (such as labeled anti-IgG antibodies) and the like. One kit is a packaged polystyrene microtiter plate coated with a SOC/CRAC polypeptide and a container containing labeled anti-human IgG antibodies. A well of the plate is contacted with, for example, serum, washed

and then contacted with the anti-IgG antibody. The label is then detected. A kit embodying features of the present invention is comprised of the following major elements: packaging an agent of the invention, a control agent, and instructions. Packaging is a box-like structure for holding a vial (or number of vials) containing an agent of the invention, a vial (or number of vials) containing a control agent, and instructions. Individuals skilled in the art can readily modify packaging to suit individual needs.

Another aspect of the invention is a method for determining the level of SOC/CRAC expression in a subject. As used herein, a subject is a human, non-human primate, cow, horse, pig, sheep, goat, dog, cat or rodent. In all embodiments, human subjects are preferred. Expression is defined either as SOC/CRAC mRNA expression or SOC/CRAC polypeptide expression. Various methods can be used to measure expression. Preferred embodiments of the invention include PCR and Northern blotting for measuring mRNA expression, and monoclonal or polyclonal SOC/CRAC antisera as reagents to measure SOC/CRAC polypeptide expression. In certain embodiments, test samples such as biopsy samples, and biological fluids such as blood, are used as test samples. SOC/CRAC expression in a test sample of a subject is compared to SOC/CRAC expression in control sample to, e.g., assess the presence or absence or stage of a proliferative disorder (e.g., a lymphocyte proliferative disorder) in a subject.

SOC/CRAC polypeptides preferably are produced recombinantly, although such polypeptides may be isolated from biological extracts. Recombinantly produced SOC/CRAC polypeptides include chimeric proteins comprising a fusion of a SOC/CRAC protein with another polypeptide, e.g., a polypeptide capable of providing or enhancing protein-protein binding, sequence specific nucleic acid binding (such as GAL4), enhancing stability of the SOC/CRAC polypeptide under assay conditions, or providing a detectable moiety, such as green fluorescent protein. A polypeptide fused to a SOC/CRAC polypeptide or fragment may also provide means of readily detecting the fusion protein, e.g., by immunological recognition or by fluorescent labeling.

The invention is also useful in the generation of transgenic non-human animals. As used herein, "transgenic non-human animals" includes non-human animals having one or more exogenous nucleic acid molecules incorporated in germ line cells and/or somatic cells. Thus the transgenic animal include "knockout" animals having a homozygous or heterozygous gene disruption by homologous recombination, animals having episomal or chromosomally incorporated expression vectors, etc. Knockout animals can be prepared by

homologous recombination using embryonic stem cells as is well known in the art. The recombination may be facilitated using, for example, the cre/lox system or other recombinase systems known to one of ordinary skill in the art. In certain embodiments, the recombinase system itself is expressed conditionally, for example, in certain tissues or cell types, at certain embryonic or post-embryonic developmental stages, inducibly by the addition of a compound which increases or decreases expression, and the like. In general, the conditional expression vectors used in such systems use a variety of promoters which confer the desired gene expression pattern (e.g., temporal or spatial). Conditional promoters also can be operably linked to SOC/CRAC nucleic acid molecules to increase expression of SOC/CRAC in a regulated or conditional manner. *Trans*-acting negative regulators of SOC/CRAC calcium channel activity or expression also can be operably linked to a conditional promoter as described above. Such *trans*-acting regulators include antisense SOC/CRAC nucleic acids molecules, nucleic acid molecules which encode dominant negative SOC/CRAC molecules, ribozyme molecules specific for SOC/CRAC nucleic acids, and the like. The transgenic non-human animals are useful in experiments directed toward testing biochemical or physiological effects of diagnostics or therapeutics for conditions characterized by increased or decreased SOC/CRAC expression. Other uses will be apparent to one of ordinary skill in the art.

The invention further provides efficient methods of identifying agents or lead compounds for agents active at the level of a SOC/CRAC polypeptide (e.g., a SOC/CRAC polypeptide) or SOC/CRAC fragment dependent cellular function. In particular, such functions include interaction with other polypeptides or fragments thereof, and selective binding to certain molecules (e.g., agonists and antagonists). Generally, the screening methods involve assaying for compounds which interfere with SOC/CRAC calcium channel activity, although compounds which enhance SOC/CRAC calcium channel activity also can be assayed using the screening methods. Such methods are adaptable to automated, high throughput screening of compounds. The target therapeutic indications for pharmacological agents detected by the screening methods are limited only in that the target cellular function be subject to modulation by alteration of the formation of a complex comprising a SOC/CRAC polypeptide or fragment thereof and one or more SOC/CRAC binding targets. Target indications include cellular processes modulated by SOC/CRAC such as Ca^{2+} fluxing, and affected by SOC/CRAC ability to form complexes with other molecules and polypeptides as, for example, may be present in the cell membrane.

A wide variety of assays for pharmacological agents are provided, including, expression assays, labeled *in vitro* protein-protein binding assays, electrophoretic mobility shift assays, immunoassays, cell-based assays such as calcium transport assays, etc. For example, two-hybrid screens are used to rapidly examine the effect of transfected nucleic acids on the intracellular binding of SOC/CRAC or SOC/CRAC fragments to specific intracellular targets (e.g. a tyrosine kinase). The transfected nucleic acids can encode, for example, combinatorial peptide libraries or cDNA libraries. Convenient reagents for such assays, e.g., GAL4 fusion proteins, are known in the art. An exemplary cell-based assay involves transfecting a cell with a nucleic acid encoding a SOC/CRAC polypeptide fused to a GAL4 DNA binding domain and a nucleic acid encoding a reporter gene operably linked to a gene expression regulatory region, such as one or more GAL4 binding sites. Activation of reporter gene transcription occurs when the SOC/CRAC and reporter fusion polypeptides bind such as to enable transcription of the reporter gene. Agents which modulate a SOC/CRAC polypeptide mediated cell function are then detected through a change in the expression of reporter gene. Methods for determining changes in the expression of a reporter gene are known in the art.

In an expression system, for example, a SOC/CRAC polypeptide is attached to a membrane, the membrane preferably separating two fluid environments and being otherwise not permeable to Ca^{2+} . Such separation is preferred so that a change in Ca^{2+} concentration on either side of the membrane is mediated only through the attached SOC/CRAC polypeptide. Preferably, a SOC/CRAC polypeptide is expressed in an intact cell and is present on the cell-membrane (as in physiologic conditions). The cell expressing the SOC/CRAC polypeptide is preferably a eukaryotic cell, and the SOC/CRAC polypeptide is preferably recombinantly expressed, although cells naturally expressing a SOC/CRAC polypeptide may also be used. Synthetic membranes, however, containing SOC/CRAC polypeptides may also be used. See, e.g., K. Kiselyov, et al., Functional interaction between InsP3 receptors and store-operated Htrp3 channels, Nature 396, 478-82 (1998).

The cell expressing the SOC/CRAC polypeptide is incubated under conditions which, in the absence of the candidate agent, permit calcium flux into the cell and allow detection of a reference calcium concentration. For example, depletion of intracellular calcium stores with thapsigargin or other agents (Putney, J.W. Jr., in Capacitative Calcium Entry, R.G. Landes Co. and Chapman & Hall, 1997) would produce a given level of SOC/CRAC channel activation and a given reference calcium concentration. Detection of a decrease in the

foregoing activities (i.e., a decrease in the intracellular calcium concentration) relative to the reference calcium concentration indicates that the candidate agent is a lead compound for an agent to inhibit SOC/CRAC calcium channel activity. Preferred SOC/CRAC polypeptides include the polypeptides of claim 15.

5 SOC/CRAC fragments used in the methods, when not produced by a transfected nucleic acid are added to an assay mixture as an isolated polypeptide. SOC/CRAC polypeptides preferably are produced recombinantly, although such polypeptides may be isolated from biological extracts or chemically synthesized. Recombinantly produced SOC/CRAC polypeptides include chimeric proteins comprising a fusion of a SOC/CRAC
10 protein with another polypeptide, e.g., a polypeptide capable of providing or enhancing protein-protein binding, sequence specific nucleic acid binding (such as GAL4), enhancing stability of the SOC/CRAC polypeptide under assay conditions, or providing a detectable moiety, such as green fluorescent protein or Flag epitope.

The assay mixture is comprised of a SOC/CRAC polypeptide binding target
15 (candidate agent) capable of interacting with a SOC/CRAC polypeptide. While natural SOC/CRAC binding targets may be used, it is frequently preferred to use portions (e.g., peptides or nucleic acid fragments) or analogs (i.e., agents which mimic the SOC/CRAC binding properties of the natural binding target for purposes of the assay) of the SOC/CRAC binding target so long as the portion or analog provides binding affinity and avidity to the
20 SOC/CRAC polypeptide (or fragment thereof) measurable in the assay.

The assay mixture also comprises a candidate agent (binding target, e.g., agonist/antagonist). Typically, a plurality of assay mixtures are run in parallel with different agent concentrations to obtain a different response to the various concentrations. Typically, one of these concentrations serves as a negative control, i.e., at zero concentration of agent or
25 at a concentration of agent below the limits of assay detection. Candidate agents encompass numerous chemical classes, although typically they are organic compounds. Preferably, the candidate agents are small organic compounds, i.e., those having a molecular weight of more than 50 yet less than about 2500, preferably less than about 1000 and, more preferably, less than about 500. Candidate agents comprise functional chemical groups necessary for
30 structural interactions with polypeptides and/or nucleic acids, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups and more preferably at least three of the functional chemical groups. The candidate agents can comprise cyclic carbon or heterocyclic structure and/or aromatic or

polyaromatic structures substituted with one or more of the above-identified functional groups. Candidate agents also can be biomolecules such as peptides, saccharides, fatty acids, sterols, isoprenoids, purines, pyrimidines, derivatives or structural analogs of the above, or combinations thereof and the like. Where the agent is a nucleic acid, the agent typically is a DNA or RNA molecule, although modified nucleic acids as defined herein are also contemplated.

Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides, synthetic organic combinatorial libraries, phage display libraries of random peptides, and the like. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural and synthetically produced libraries and compounds can be readily modified through conventional chemical, physical, and biochemical means. Further, known agents may be subjected to directed or random chemical modifications such as acylation, alkylation, esterification, amidification, etc. to produce structural analogs of the agents. Non-SOC/CRAC calcium channel agonists and antagonists, for example, include agents such as dihydropyridines (DHPs), phenylalkylamines, omega conotoxin (omega.-CgTx) and pyrazonoylguanidines.

A variety of other reagents also can be included in the mixture. These include reagents such as salts, buffers, neutral proteins (e.g., albumin), detergents, etc. which may be used to facilitate optimal protein-protein, protein-nucleic acid, and/or protein/membrane component binding association. Such a reagent may also reduce non-specific or background interactions of the reaction components. Other reagents that improve the efficiency of the assay such as protease, inhibitors, nuclease inhibitors, antimicrobial agents, and the like may also be used.

The mixture of the foregoing assay materials is incubated under conditions whereby, but for the presence of the candidate agent, the SOC/CRAC polypeptide specifically binds the cellular binding target, a portion thereof or analog thereof. The order of addition of components, incubation temperature, time of incubation, and other perimeters of the assay may be readily determined. Such experimentation merely involves optimization of the assay parameters, not the fundamental composition of the assay. Incubation temperatures typically

are between 4°C and 40°C. Incubation times preferably are minimized to facilitate rapid, high throughput screening, and typically are between 0.1 and 10 hours.

After incubation, the presence or absence of specific binding between the SOC/CRAC polypeptide and one or more binding targets is detected by any convenient method available to the user. For cell free binding type assays, a separation step is often used to separate bound from unbound components. The separation step may be accomplished in a variety of ways. Conveniently, at least one of the components is immobilized on a solid substrate, from which the unbound components may be easily separated. The solid substrate can be made of a wide variety of materials and in a wide variety of shapes, e.g., microtiter plate, microbead, dipstick, resin particle, etc. The substrate preferably is chosen to maximum signal to noise ratios, primarily to minimize background binding, as well as for ease of separation and cost.

Separation may be effected for example, by removing a bead or dipstick from a reservoir, emptying or diluting a reservoir such as a microtiter plate well, rinsing a bead, particle, chromatographic column or filter with a wash solution or solvent. The separation step preferably includes multiple rinses or washes. For example, when the solid substrate is a microtiter plate, the wells may be washed several times with a washing solution, which typically includes those components of the incubation mixture that do not participate in specific bindings such as salts, buffer, detergent, non-specific protein, etc. Where the solid substrate is a magnetic bead, the beads may be washed one or more times with a washing solution and isolated using a magnet.

Detection may be effected in any convenient way for cell-based assays such as two- or three-hybrid screens. The transcript resulting from a reporter gene transcription assay of SOC/CRAC polypeptide interacting with a target molecule typically encodes a directly or indirectly detectable product, e.g., β -galactosidase activity, luciferase activity, and the like. For cell-free binding assays, one of the components usually comprises, or is coupled to, a detectable label. A wide variety of labels can be used, such as those that provide direct detection (e.g., radioactivity, luminescence, optical or electron density, etc.) or indirect detection (e.g., epitope tag such as the FLAG epitope, enzyme tag such as horseradish peroxidase, etc.). The label may be bound to a SOC/CRAC binding partner, or incorporated into the structure of the binding partner.

A variety of methods may be used to detect the label, depending on the nature of the label and other assay components. For example, the label may be detected while bound to the solid substrate or subsequent to separation from the solid substrate. Labels may be directly

detected through optical or electron density, radioactive emissions, nonradiative energy transfers, etc. or indirectly detected with antibody conjugates, strepavidin-biotin conjugates, etc. Methods for detecting the labels are well known in the art.

Of particular importance in any of the foregoing assays and binding studies is the use of a specific sequence motif identified in the SOC-2/CRAC-1 polypeptide sequence as a kinase catalytic domain. According to the invention, amino acids 999-1180 of the SOC-2/CRAC-1 polypeptide (SEQ ID NO:24) (or a fragment thereof), show a localized homology with the catalytic domains of eukaryotic elongation factor-2 kinase (eEF-2 kinase, GenBank Acc. no. U93850) and *Dictyostelium* myocin heavy chain kinase A (MHCK A, GenBank Acc. no. U16856), as disclosed in Ryazanov AG, et al., *Proc Natl Acad Sci U S A*, 1997, 94(10):4884-4889. Therefore, according to the invention, a method for identifying agents useful in the modulation of SOC/CRAC polypeptide kinase activity is provided. The method involves contacting a SOC/CRAC polypeptide with kinase activity, that includes, for example, amino acids 999-1180 of the SOC-2/CRAC-1 polypeptide (SEQ ID NO:24) with a candidate agent suspected of modulating SOC/CRAC kinase activity, under conditions sufficient to allow the candidate agent to interact with the SOC/CRAC polypeptide and modulate its kinase activity; detecting a kinase activity associated with the SOC/CRAC polypeptide in the presence of the candidate agent; and comparing the kinase activity in the previous step with a control kinase activity of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the candidate agent modulates (increases or decreases) SOC/CRAC kinase activity. Other controls for kinase activity can also be performed at the same time, for example, by utilizing eEF-2 kinase and/or *Dictyostelium* MHC Kinase A, in a similar manner to the SOC/CRAC member. Methods for performing such kinase activity assays are well known in the art.

The invention thus provides SOC/CRAC-specific binding agents, methods of identifying and making such agents, and their use in diagnosis, therapy and pharmaceutical development. For example, SOC/CRAC-specific agents are useful in a variety of diagnostic and therapeutic applications, especially where disease or disease prognosis is associated with altered SOC/CRAC and SOC/CRAC calcium channel fluxing characteristics. Novel SOC/CRAC-specific binding agents include SOC/CRAC-specific antibodies and other natural intracellular and extracellular binding agents identified with assays such as two hybrid screens, and non-natural intracellular and extracellular binding agents identified in screens of chemical libraries and the like.

In general, the specificity of SOC/CRAC binding to a specific molecule is determined by binding equilibrium constants. Targets which are capable of selectively binding a SOC/CRAC polypeptide preferably have binding equilibrium constants of at least about 10^7 M^{-1} , more preferably at least about 10^8 M^{-1} , and most preferably at least about 10^9 M^{-1} . The wide variety of cell based and cell free assays may be used to demonstrate SOC/CRAC-specific binding. Cell based assays include one, two and three hybrid screens, assays in which SOC/CRAC-mediated transcription is inhibited or increased, etc. Cell free assays include SOC/CRAC-protein binding assays, immunoassays, etc. Other assays useful for screening agents which bind SOC/CRAC polypeptides include fluorescence resonance energy transfer (FRET), and electrophoretic mobility shift analysis (EMSA).

Various techniques may be employed for introducing nucleic acids of the invention into cells, depending on whether the nucleic acids are introduced *in vitro* or *in vivo* in a host. Such techniques include transfection of nucleic acid- $CaPO_4$ precipitates, transfection of nucleic acids associated with DEAE, transfection with a retrovirus including the nucleic acid of interest, liposome mediated transfection, and the like. For certain uses, it is preferred to target the nucleic acid to particular cells. In such instances, a vehicle used for delivering a nucleic acid of the invention into a cell (e.g., a retrovirus, or other virus; a liposome) can have a targeting molecule attached thereto. For example, a molecule such as an antibody specific for a surface membrane protein on the target cell or a ligand for a receptor on the target cell can be bound to or incorporated within the nucleic acid delivery vehicle. For example, where liposomes are employed to deliver the nucleic acids of the invention, proteins which bind to a surface membrane protein associated with endocytosis may be incorporated into the liposome formulation for targeting and/or to facilitate uptake. Such proteins include capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half life, and the like. Polymeric delivery systems also have been used successfully to deliver nucleic acids into cells, as is known by those skilled in the art. Such systems even permit oral delivery of nucleic acids.

Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the anti-inflammatory agent, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer base systems such as poly(lactide-glycolide), copolyoxalates, polycaprolactones,

-41-

polyesteramides, polyorthoesters, polyhydroxybutyric acid, and polyanhydrides. Microcapsules of the foregoing polymers containing drugs are described in, for example, U.S. Patent 5,075,109. Delivery systems also include non-polymer systems that are: lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono- di- and tri-glycerides; hydrogel release systems; sylastic systems; peptide based systems; wax coatings; compressed tablets using conventional binders and excipients; partially fused implants; and the like. Specific examples include, but are not limited to: (a) erosional systems in which an agent of the invention is contained in a form within a matrix such as those described in U.S. Patent Nos. 4,452,775, 4,675,189, and 5,736,152, and (b) diffusional systems in which an active component permeates at a controlled rate from a polymer such as described in U.S. Patent Nos. 3,854,480, 5,133,974 and 5,407,686. In addition, pump-based hardware delivery systems can be used, some of which are adapted for implantation.

Use of a long-term sustained release implant may be particularly suitable for treatment of chronic conditions. Long-term release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 30 days, and preferably 60 days. Long-term sustained release implants are well-known to those of ordinary skill in the art and include some of the release systems described above.

The invention also contemplates gene therapy. The procedure for performing *ex vivo* gene therapy is outlined in U.S. Patent 5,399,346 and in exhibits submitted in the file history of that patent, all of which are publicly available documents. In general, it involves introduction *in vitro* of a functional copy of a gene into a cell(s) of a subject which contains a defective copy of the gene, and returning the genetically engineered cell(s) to the subject. The functional copy of the gene is under operable control of regulatory elements which permit expression of the gene in the genetically engineered cell(s). Numerous transfection and transduction techniques as well as appropriate expression vectors are well known to those of ordinary skill in the art, some of which are described in PCT application WO95/00654. *In vivo* gene therapy using vectors such as adenovirus, retroviruses, herpes virus, and targeted liposomes also is contemplated according to the invention. See, e.g., U.S. Patent Nos. 5,670,488, entitled "Adenovirus Vector for Gene Therapy", issued to Gregory et al., and 5,672,344, entitled "Viral-Mediated Gene Transfer System", issued to Kelley et al.

The invention will be more fully understood by reference to the following examples. These examples, however, are merely intended to illustrate the embodiments of the invention and are not to be construed to limit the scope of the invention.

Examples

5 As an initial approach to identifying SOC/CRAC channels, we considered publicly available data and hypothesized that the following characteristics are likely to be exhibited by SOC/CRAC calcium channels: i) SOC/CRAC calcium channels would be integral membrane proteins related (probably distantly) to one of the known calcium channel families (e.g. voltage gated, ligand gated, Trp), and therefore should have a pore region formed by a tetramer of 6-7 transmembrane (TM) regions; ii) high calcium selectivity was likely to come
10 at the price of complexity, and therefore these were likely to be large proteins; iii) the high calcium selectivity of this type of channel was likely to be useful and, therefore, highly conserved; and iv) these channels should be expressed in one or more types of lymphocytes, since ICRAC is best defined in those cell types. Since the full genome of the nematode *C. elegans* is nearing completion, and IP3-dependent calcium signals have recently been shown
15 to be required for one or more aspects of *C. elegans* development, we took the set of proteins encoded by this genome (at the time this search was initiated WORMPEP14 was the available predicted protein set) and began searching for proteins which fit the criteria above. This search began by proceeding in alphabetical order through WORMPEP14 and arbitrarily
20 excluding all proteins below approximately 1000 amino acids in size, followed by focusing on remaining proteins with clear TM spanning regions similar to those of other calcium channels. We stopped this screen on encountering a protein designated C05C12.3, a predicted protein of 1816 amino acids (SEQ ID NO:13). C05C12.3 was notable because its central pore region had some sequence similarity to but was clearly distinct from members of the Trp
25 family of calcium channels, and the hydrophobicity plot of this region showed a characteristically wide spacing between the fifth and sixth TM regions for the amino acid residues which are thought to line the channel pore region and mediate the calcium selectivity of the channels. In addition, it lacked any ankyrin repeats in the region amino-terminal to its pore region, further distinguishing it from other Trp family proteins.

30 We then used C05C12.3 for BLAST alignment screening of the rest of the *C. elegans* genome and also mammalian databases for homologous proteins, revealing two other *C. elegans* homologues (SEQ ID NO:14 and SEQ ID NO:15), and also a recently cloned mammalian protein named melastatin-1 (MLSN-1/SOC-1, SEQ ID NOs:9 and 10, and

GenBank Acc. No. AF071787). Using these sequences, we subsequently performed an exhaustive screening of publicly accessible EST databases in search of lymphocyte homologues, but were unsuccessful in detecting any homologous transcripts in any lymphocyte lines. Since MLSN-1 (SEQ ID NOs:9 and 10) was expressed exclusively in melanocytes and retina by Northern blot hybridization and by EST database searching, there was no evidence that this type of channel was expressed in the type of cell in which ICRAC-like currents were best defined. Subsequent BLAST searches picked up mouse EST sequence AI098310 (SEQ ID NO:22) from a monocyte cell line. The I.M.A.G.E. consortium clone containing the above-identified EST was then purchased from ATCC (clone ID. 1312756, Manassas, VA) and was further characterized. Using other portions of this sequence in EST searches, we subsequently picked up similar sequences in human B-cells (SEQ ID NOs:20 and 21), and other cell types as well (SEQ ID NOs: 11, 12, 16, 17, 18, and 19). Most of these sequences were subsequently identified to be part of the 3'-UTR or of the carboxy terminal region of the proteins, which are not readily identifiable as Trp channels, providing an explanation for the art's inability to detect any type of Trp related transcripts in lymphocytes. Partial sequences from the 5' and/or 3' ends of the above identified clones were then used to screen leukocyte and kidney cDNA libraries to extend the original sequences more toward the 5' and/or 3' ends.

In view of the foregoing, it was concluded that channels of this type were expressed in many types of lymphocytes, and therefore were members of a new family of SOC/CRAC calcium channels.

Experimental Procedures

Screening of the cDNA libraries

Leukocyte and kidney cDNA libraries from Life Technologies (Gaithersburg, MD) were screened using the Gene Trapper II methodology (Life Technologies) according to manufacturer's recommendation, using the inserts of I.M.A.G.E. clone ID nos. 1312756 and 1076485 from ATCC (Manassas, VA), under stringent hybridization conditions. Using standard methodology (*Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or *Current Protocols in Molecular Biology*, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York), individual cDNA clones were subjected to 3-4 rounds of amplification and purification under the same hybridization conditions.

After excision from the vector and subcloning of inserts into the plasmid forms, several clones were sequenced by the Beth Israel Deaconess Medical Center's Automated

-44-

Sequencing Facility. Molecular biological techniques such as restriction enzyme treatment, subcloning, DNA extraction, bacterial culture and purification of DNA fragments were performed according to methods well known in the art. Computer analyses of protein and DNA sequences was done using "Assemblylign" (Oxford Molecular, Campbell, CA). Multiple
5 alignments of the SOC/CRAC family members were produced using the CLUSTAL facility of the MacVector program. Restriction endonucleases, expression vectors, and modifying enzymes were purchased from commercial sources (Gibco-BRL). Sequencing vectors for DNA were purchased from Stratagene (La Jolla, CA).

Once the first members of what appeared to be a novel family of calcium channel
10 receptors were identified and characterized, additional BLAST alignments were performed with the newly characterized nucleic acid sequences. An initial match was with genomic DNA fragment NH0332L11 (Genbank Acc. No. AC005538). Using this genomic sequence, promoters were designed and a number of cDNA libraries was surveyed by PCR. A prostate specific message was identified and characterized, leading to the isolation and
15 characterization of SOC-4/CRAC-3 (SEQ ID NOs: 31 and 32).

Functional Assays

Transient Expression of SOC/CRAC

In our initial transient expression experiments, we expressed or expect to express a SOC/CRAC molecule transiently in RBL-2H3 mast cells, Jurkat T cells, and A20
20 B-lymphocytes using both electroporation and vaccinia virus-driven expression, and measured the calcium influx produced by depletion of intracellular calcium stores with thapsigargin. Each of the foregoing techniques is well known to those of ordinary skill in the art and can be performed using various methods (see, e.g., Current Methods in Molecular Biology, eds. Ausubal, F.M., et al. 1987, Green Publishers and Wiley Interscience, N.Y.,
25 N.Y.). Exemplary methods are described herein.

Depletion of intracellular calcium stores is accomplished by treating the cells with 1 micromolar thapsigargin; alternative agents which function to deplete intracellular stores are described in by Putney, J.W. Jr., in Capacitative Calcium Entry, R.G. Landes Co. and Chapman & Hall, 1997 and include, for example, ionomycin, cyclopiazonic acid, and DBHQ.

30 Calcium influx is determined by measuring cytoplasmic calcium as indicated using the fura-2 fluorescent calcium indicator (see, e.g., G. Grynkiewicz, M. Poenie, R. Y. Tsien, A new generation of Ca²⁺ indicators with greatly improved fluorescence properties, J. Biol

Chem 260, 3440-50 (1985), and M. Poenie, R. Tsien, Fura-2: a powerful new tool for measuring and imaging $[Ca^{2+}]_i$ in single cells, Prog Clin Biol Res 210, 53-6 (1986)).

Patch Clamp Analysis and Determining Selectivity of SOC/CRAC

Patch clamp analysis of cells injected with SOC/CRAC cRNA is performed by using the general patch technique as described in Neher, E., "Ion channels for communication between and within cells", Science, 1992; 256:498-502. Specific techniques for applying the patch clamp analysis to RBL cells are described in Hoth, M., and Penner, R., "Depletion of intracellular calcium stores activates a calcium current in mast cells", Nature, 1992; 355:3535-355. Additional protocols for applying the patch clamp technique to other cell types are described in Putney, J.W. Jr., in Capacitative Calcium Entry, R.G. Landes Co. and Chapman & Hall, 1997

An exemplary protocol for patch clamp analysis of SOC/CRAC molecule expressed in RBL-2H3 mast cells using a recombinant vaccinia virus is as follows. The currents elicited by store depletion are determined using the whole cell configuration (Neher, E., Science, 1992; 256:498-502). Currents in SOC/CRAC expressing cells are compared to currents in control cells expressing an irrelevant protein or a classic Trp family calcium channel known as VR1 (M. J. Caterina, et al., The capsaicin receptor: a heat-activated ion channel in the pain pathway [see comments], Nature 389, 816-24 (1997)) in order to assess the contribution of SOC/CRAC expression. In addition, the magnitude of whole cell currents in the presence of extracellular calcium (10 mM), barium (10 mM), or magnesium (10 mM) are compared to determine the relative permeability of the channels to each of these ions (Hoth, M., and Penner, R., Nature, 1992; 355:3535-355) and, thereby, determine the ionic selectivity.

Pharmacologic Behavior of SOC/CRAC

For analysis of the pharmacologic behavior of a SOC/CRAC molecule, a SOC/CRAC molecule is expressed in RBL-2H3 mast cells using a recombinant vaccinia virus, and the degree of calcium influx elicited by store depletion is monitored using a bulk spectrofluorimeter or a fluorescence microscope and the calcium sensitive dye fura-2 (G. Grynkiewicz, M. Poenie, R. Y. Tsien, A new generation of Ca^{2+} indicators with greatly improved fluorescence properties, J Biol Chem 260, 3440-50 (1985) and M. Poenie, R. Tsien, Fura-2: a powerful new tool for measuring and imaging $[Ca^{2+}]_i$ in single cells, Prog Clin Biol Res 210, 53-6 (1986)). The level of cytoplasmic calcium in SOC/CRAC expressing cells is compared to the level achieved in control cells expressing an irrelevant protein or a classic Trp. family calcium channels known as VR1 (M. J. Caterina, et al., The

capsaicin receptor: a heat-activated ion channel in the pain pathway [see comments], Nature 389, 816-24 (1997)). These cells then are pre-incubated with the desired pharmacologic reagent, and again the response to store depletion is monitored. Comparison of the effect of depleting stores in SOC/CRAC expressing cells relative to controls in the presence or absence of the pharmacologic reagent is used to assess the ability of that reagent to modulate SOC/CRAC activity. Sphingosine is an exemplary molecule that can be used as pharmacologic reagents for pharmacologic characterization of SOC/CRAC calcium channels. See, e.g., Mathes, C., et al., Calcium release activated calcium current as a direct target for sphingosine, J Biol Chem 273(39):25020-25030 (1998). Other non-specific calcium channel inhibitors that can be used for this purpose include SKR96365 (Calbiochem) and Lanthanum.

Bulk Calcium Assays

Bulk calcium assays can be performed in a PTI Deltascan bulk spectrofluorometer using fura-2 as described in Scharenberg AM, et al., EMBO J, 1995, 14(14):3385-94.

Gene Targeting

The method (and reagents) described by Buerstedde JM et al, (Cell, 1991, Oct 4;67(1):179-88), was used to generate "knockouts" in cells. Briefly, part of the chicken SOC-2/CRAC-1 genomic sequence coding for the transmembrane region was cloned utilizing the human sequence as the probe in a chicken library screen. Chicken SOC-2/CRAC-1 clones were isolated and characterized using standard methodology. The putative exon and domain arrangement of the chicken SOC-2/CRAC-1, is depicted in Figure 1. The exons coding for TM5 (pore region) and TM6, were replaced with promoter/antibiotic cassettes (see Figure1). These targeting vectors were then used to target (and replace) the endogenous gene in DT-40 cells (chicken B lymphocyte cells).

Results

Example 1: Transient Expression of SOC/CRAC

In the above-identified cell lines and using both of the foregoing expression techniques, SOC/CRAC expression enhances thapsigargin-dependent influx. In addition, SOC/CRAC expression also enhances the amount of intracellular calcium stores. That this effect is likely due to SOC/CRAC acting as a plasma membrane calcium channel can be confirmed by producing an in-frame carboxy-terminal translational fusion with green fluorescent protein followed by confocal microscopy, revealing that SOC/CRAC is expressed predominantly as a plasma membrane calcium channel.

Example 2: Patch Clamp Analysis

The biophysical characteristics of SOC/CRAC enhanced currents when expressed in *Xenopus* oocytes are determined. SOC/CRAC cRNA injection is able to enhance thapsigargin-dependent whole cell currents. In addition, SOC/CRAC does not alter the reversal potential of these currents and the determination of the P_{Ca}/P_{Na} ratio shows that SOC/CRAC channels are highly calcium selective.

Example 3: *Pharmacologic Behavior of SOC/CRAC*

The pharmacologic behavior of SOC/CRAC is evaluated as described above. SOC/CRAC-enhanced influx is inhibited by sphingosine in a manner that is substantially the same as that of endogenous thapsigargin-dependent calcium influx.

Example 4: *Gene targeting*

Transfection of DT-40 cells with the foregoing targeting vectors, selection for antibiotic resistance, and screening, is collectively referred to, herein, as a round of targeting. For the first round of targeting SOC-2/CRAC-1, 18/24 clones with homologous recombination of the targeting construct into one of the endogenous SOC-2/CRAC-1 alleles were obtained. On the second round of targeting (in order to target the second allele and therefore generate a homozygous SOC-2/CRAC-1 mutant cell), 0/48 clones were obtained. These results indicate that a "null" SOC-2/CRAC-1 mutation is detrimental to DT-40 cells, and that SOC-2/CRAC-1 is required for cell viability.

Table I. Nucleotide Sequences with homologies to SOC/CRAC nucleic acids

Sequences with SEQ ID NOs and GenBank accession numbers:
SEQ ID NO:9, AB001535, AI226731, H18835, AA419592, AA261842, AA419407, AA592910, D86107, AI098310, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, AC005538, AA654650, AA370110, AA313170, AA493512, AI670079, AI671853.

Table II. Amino Acid Sequences with homologies to SOC/CRAC polypeptides

Sequences with SEQ ID NOs and GenBank accession numbers:
SEQ ID NO:10, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, AB001535, AA592910, D86107, AF071787, Z77132, Z83117, Z68333, AA708532, AA551759, AA932133, R47363, N31660, NP003298, CAB00861, NP002411, CAA92726, CAB05572.

All references, patents, and patent documents disclosed herein are incorporated by reference herein in their entirety.

What is claimed is presented below and is followed by a Sequence Listing. We claim:

Claims

1. An isolated nucleic acid molecule, comprising:

(a) nucleic acid molecules which hybridize under stringent conditions to a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31, and which code for a SOC/CRAC polypeptide;

(b) deletions, additions and substitutions of (a) which code for a respective SOC/CRAC polypeptide;

(c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) in codon sequence due to the degeneracy of the genetic code, and

(d) complements of (a), (b) or (c).

2. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:1.

3. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:27.

4. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:29.

5. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:31.

6. An isolated nucleic acid molecule selected from the group consisting of

(a) a unique fragment of a nucleic acid molecule selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:29, and SEQ ID NO:31,

(b) complements of (a),
provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to any sequence selected from a sequence group consisting of

(1) sequences having the SEQ. ID NOS. or GenBank accession numbers of Table I,

(2) complements of (1), and

(3) fragments of (1) and (2).

7. The isolated nucleic acid molecule of claim 6, wherein the sequence of contiguous nucleotides is selected from the group consisting of:

- (1) at least two contiguous nucleotides nonidentical to the sequence group,
- (2) at least three contiguous nucleotides nonidentical to the sequence group,
- 5 (3) at least four contiguous nucleotides nonidentical to the sequence group,
- (4) at least five contiguous nucleotides nonidentical to the sequence group,
- (5) at least six contiguous nucleotides nonidentical to the sequence group,
- (6) at least seven contiguous nucleotides nonidentical to the sequence group.

10 8. The isolated nucleic acid molecule of claim 6, wherein the unique fragment has a size selected from the group consisting of at least: 8 nucleotides, 10 nucleotides, 12 nucleotides, 14 nucleotides, 16 nucleotides, 18 nucleotides, 20, nucleotides, 22 nucleotides, 24 nucleotides, 26 nucleotides, 28 nucleotides, 30 nucleotides, 50 nucleotides, 75 nucleotides, 100 nucleotides, and 200 nucleotides.

15 9. The isolated nucleic acid molecule of claim 6, wherein the molecule encodes a polypeptide which is immunogenic.

10. An expression vector comprising the isolated nucleic acid molecule of claims 1, 2, 3, 4, 5, 6, 7, 8, or 9 operably linked to a promoter.

11. A host cell transformed or transfected with the expression vector of claim 10.

20 12. An isolated polypeptide encoded by the isolated nucleic acid molecule according to anyone of claims 1 or 6, wherein the polypeptide comprises a SOC/CRAC polypeptide or a unique fragment thereof.

13. The isolated polypeptide of claim 12, wherein the isolated polypeptide is encoded by the isolated nucleic acid molecule of claim 2, 3, 4, or 5.

25 14. The isolated polypeptide of claim 13, wherein the isolated polypeptide comprises a polypeptide having the sequence of amino acids selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32.

-50-

15. An isolated polypeptide encoded by the isolated nucleic acid molecule of claim 1, 2, 3, 4, or 5, wherein the polypeptide, or unique fragment thereof is immunogenic.

16. An isolated binding polypeptide which binds selectively to a polypeptide encoded by the isolated nucleic acid molecule of claim 1, 2, 3, 4, or 5.

5 17. The isolated binding polypeptide of claim 16, wherein the isolated binding polypeptide binds to a polypeptide having the sequence of amino acids selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32.

10 18. The isolated binding polypeptide of claim 17, wherein the isolated binding polypeptide is an antibody or an antibody fragment selected from the group consisting of a Fab fragment, a F(ab)₂ fragment or a fragment including a CDR3 region selective for the polypeptide.

15 19. An isolated polypeptide, comprising a unique fragment of the polypeptide of claim 12 of sufficient length to represent a sequence unique within the human genome, provided that the fragment excludes a sequence of contiguous amino acids identified in Table II.

20. A method for isolating a SOC/CRAC molecule having SOC/CRAC calcium channel activity, comprising:

20 a) contacting a binding molecule that is a SOC/CRAC nucleic acid or a SOC/CRAC binding polypeptide with a sample containing one or more SOC/CRAC molecules, under conditions sufficient to form a complex of the SOC/CRAC nucleic acid or the SOC/CRAC binding polypeptide and the SOC/CRAC molecule;

b) detecting the presence of the complex;

c) isolating the SOC/CRAC molecule from the complex; and

25 d) determining whether the isolated SOC/CRAC molecule has SOC/CRAC calcium channel activity.

21. The method of claim 20, wherein the binding molecule is a SOC/CRAC nucleic acid.

22. The method of claim 20, wherein the binding molecule is a SOC/CRAC binding polypeptide.

23. The method of claim 21, wherein the SOC/CRAC nucleic acid comprises at least 14 nucleotides from any contiguous portion of a sequence of nucleotides selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31.

5 24. A method for identifying agents useful in the modulation of SOC/CRAC calcium channel activity, comprising:

a) contacting a SOC/CRAC polypeptide with a candidate agent suspected of modulating SOC/CRAC calcium channel activity, under conditions sufficient to allow the SOC/CRAC polypeptide to interact selectively with the candidate agent;

10 b) detecting a Ca^{2+} concentration associated with SOC/CRAC calcium channel activity of the SOC/CRAC polypeptide in the presence of the candidate agent; and

c) comparing the Ca^{2+} concentration of step (b) with a control Ca^{2+} concentration of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the candidate agent modulates SOC/CRAC calcium channel activity.

15

25. A method for determining the level of SOC/CRAC expression in a subject, comprising:

a) measuring the expression of SOC/CRAC in a test sample obtained from the subject, and

20 b) comparing the measured expression of SOC/CRAC in the test sample to the expression of the SOC/CRAC polypeptide in a control to determine the level of SOC/CRAC expression in the subject.

25

26. The method of claim 25, wherein the expression of SOC/CRAC in (b) is SOC/CRAC mRNA expression.

27. The method of claim 25, wherein the expression of SOC/CRAC in (b) is SOC/CRAC polypeptide expression.

28. The method of claim 25, wherein the test sample is tissue.

29. The method of claim 25, wherein the test sample is a biological fluid.

30. The method of claim 26, wherein SOC/CRAC mRNA expression is measured using the Polymerase Chain Reaction (PCR).

31. The method of claim 26, wherein SOC/CRAC mRNA expression is measured using a method selected from the group consisting of northern blotting, monoclonal antisera to
5 SOC/CRAC and polyclonal antisera to SOC/CRAC.

32. A kit, comprising a package containing:

an agent that selectively binds to the isolated nucleic acid of claim 1 or an expression product thereof, and

10 a control for comparing to a measured value of binding of said agent to said isolated nucleic acid of claim 1 or expression product thereof.

33. The kit of claim 32, wherein the control comprises an epitope of the expression product of the nucleic acid of claim 1.

34. A pharmaceutical composition comprising:

15 a pharmaceutically effective amount of an agent comprising of an isolated nucleic acid molecule of claim 1 or an expression product thereof, and

a pharmaceutically acceptable carrier.

35. The pharmaceutical composition of claim 34, wherein the agent is an expression product of the isolated nucleic acid molecule of claim 1.

20 36. A method for identifying agents useful in the modulation of a SOC/CRAC polypeptide kinase activity, comprising:

a) contacting a SOC/CRAC polypeptide with kinase activity with a candidate agent suspected of modulating SOC/CRAC kinase activity, under conditions sufficient to allow the
25 candidate agent to interact with the SOC/CRAC polypeptide and modulate its kinase activity;

b) detecting a kinase activity associated with the SOC/CRAC polypeptide in the presence of the candidate agent; and

c) comparing the kinase activity of step (b) with a control kinase activity of a SOC/CRAC polypeptide in the absence of the candidate agent to determine whether the
30 candidate agent modulates SOC/CRAC kinase activity.

37. The method of claim 36, wherein the SOC/CRAC polypeptide comprises amino acids 999-1180 of the sequence represented as SEQ ID NO:24, or a fragment thereof that retains the kinase activity.

1/1

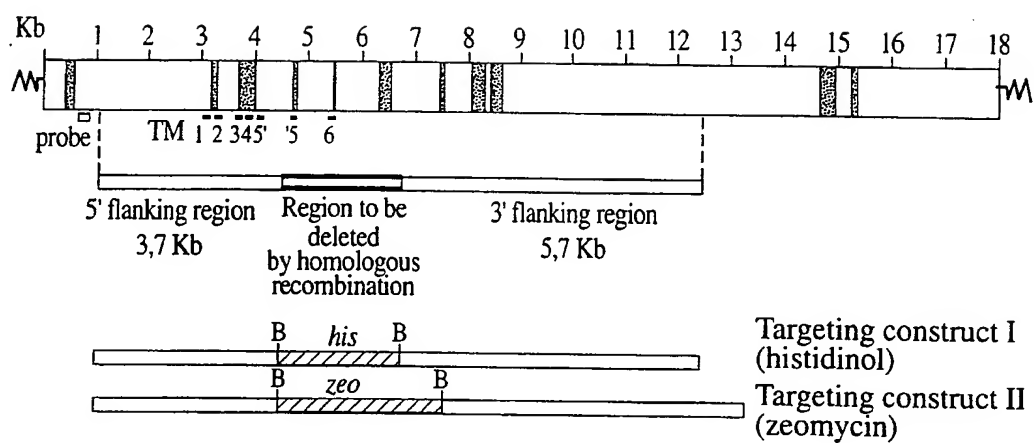


Fig. 1

-1-

SEQUENCE LISTING

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Scharenberg, Andrew

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Cys Asn Ile Phe Gly Gln Asp Leu Pro Ala Val Pro Gln Arg Lys Glu
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-5-

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-6-

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<213> Mus Musculus

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-10-

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-12-

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gccactgagc	actggccgag	gtgatgcccc	cccttccctg	gacaggcctc	tgtcttccac	6180
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<210> 12

<211> 1503

-15-

<212> PRT

<213> Homo Sapiens

<400> 12

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Phe Glu Gly Leu Pro Arg Arg Val Thr Asp Leu Gly Met Val Ser Asn
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Leu Arg Arg Ser Asn Ser Ser Leu Phe Lys Ser Trp Arg Leu Gln Cys
          35          40          45
Pro Phe Gly Asn Asn Asp Lys Gln Glu Ser Leu Ser Ser Trp Ile Pro
          50          55          60
Glu Asn Ile Lys Lys Lys Glu Cys Val Tyr Phe Val Glu Ser Ser Lys
65          70          75          80
Leu Ser Asp Ala Gly Lys Val Val Cys Gln Cys Gly Tyr Thr His Glu
          85          90          95
Gln His Leu Glu Glu Ala Thr Lys Pro His Thr Phe Gln Gly Thr Gln
          100          105          110
Trp Asp Pro Lys Lys His Val Gln Glu Met Pro Thr Asp Ala Phe Gly
          115          120          125
Asp Ile Val Phe Thr Gly Leu Ser Gln Lys Val Lys Lys Tyr Val Arg
130          135          140
Val Ser Gln Asp Thr Pro Ser Ser Val Ile Tyr His Leu Met Thr Gln
145          150          155          160
His Trp Gly Leu Asp Val Pro Asn Leu Leu Ile Ser Val Thr Gly Gly
          165          170          175
Ala Lys Asn Phe Asn Met Lys Pro Arg Leu Lys Ser Ile Phe Arg Arg
          180          185          190
Gly Leu Val Lys Val Ala Gln Thr Thr Gly Ala Trp Ile Ile Thr Gly
          195          200          205
Gly Ser His Thr Gly Val Met Lys Gln Val Gly Glu Ala Val Arg Asp
210          215          220
Phe Ser Leu Ser Ser Ser Tyr Lys Glu Gly Glu Leu Ile Thr Ile Gly
225          230          235          240
Val Ala Thr Trp Gly Thr Val His Arg Arg Glu Gly Leu Ile His Pro
          245          250          255
Thr Gly Ser Phe Pro Ala Glu Tyr Ile Leu Asp Glu Asp Gly Gln Gly
260          265          270
Asn Leu Thr Cys Leu Asp Ser Asn His Ser His Phe Ile Leu Val Asp
          275          280          285
Asp Gly Thr His Gly Gln Tyr Gly Val Glu Ile Pro Leu Arg Thr Arg
290          295          300
Leu Glu Lys Phe Ile Ser Glu Gln Thr Lys Glu Arg Gly Gly Val Ala
305          310          315          320
Ile Lys Ile Pro Ile Val Cys Val Val Leu Glu Gly Gly Pro Gly Thr
          325          330          335
Leu His Thr Ile Asp Asn Ala Thr Thr Asn Gly Thr Pro Cys Val Val
          340          345          350
Val Glu Gly Ser Gly Arg Val Ala Asp Val Ile Ala Gln Val Ala Asn
          355          360          365
Leu Pro Val Ser Asp Ile Thr Ile Ser Leu Ile Gln Gln Lys Leu Ser
370          375          380
Val Phe Phe Gln Glu Met Phe Glu Thr Phe Thr Glu Ser Arg Ile Val
385          390          395          400
Glu Trp Thr Lys Lys Ile Gln Asp Ile Val Arg Arg Arg Gln Leu Leu
          405          410          415
Thr Val Phe Arg Glu Gly Lys Asp Gly Gln Gln Asp Val Asp Val Ala
          420          425          430
Ile Leu Gln Ala Leu Leu Lys Ala Ser Arg Ser Gln Asp His Phe Gly
          435          440          445

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-16-

His	Glu	Asn	Trp	Asp	His	Gln	Leu	Lys	Leu	Ala	Val	Ala	Trp	Asn	Arg
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Val	Asp	Ile	Ala	Arg	Ser	Glu	Ile	Phe	Met	Asp	Glu	Trp	Gln	Trp	Lys
465					470					475					480
Pro	Ser	Asp	Leu	His	Pro	Thr	Met	Thr	Ala	Ala	Leu	Ile	Ser	Asn	Lys
				485					490					495	
Pro	Glu	Phe	Val	Lys	Leu	Phe	Leu	Glu	Asn	Gly	Val	Gln	Leu	Lys	Glu
			500					505					510		
Phe	Val	Thr	Trp	Asp	Thr	Leu	Leu	Tyr	Leu	Tyr	Glu	Asn	Leu	Asp	Pro
		515				520						525			
Ser	Cys	Leu	Phe	His	Ser	Lys	Leu	Gln	Lys	Val	Leu	Val	Glu	Asp	Pro
530					535					540					
Glu	Arg	Pro	Ala	Cys	Ala	Pro	Ala	Ala	Pro	Arg	Leu	Gln	Met	His	His
545				550						555					560
Val	Ala	Gln	Val	Leu	Arg	Glu	Leu	Leu	Gly	Asp	Phe	Thr	Gln	Pro	Leu
				565					570					575	
Tyr	Pro	Arg	Pro	Arg	His	Asn	Asp	Arg	Leu	Arg	Leu	Leu	Leu	Pro	Val
			580					585					590		
Pro	His	Val	Lys	Leu	Asn	Val	Gln	Gly	Val	Ser	Leu	Arg	Ser	Leu	Tyr
		595				600						605			
Lys	Arg	Ser	Ser	Gly	His	Val	Thr	Phe	Thr	Met	Asp	Pro	Ile	Arg	Asp
610					615						620				
Leu	Leu	Ile	Trp	Ala	Ile	Val	Gln	Asn	Arg	Arg	Glu	Leu	Ala	Gly	Ile
625				630						635					640
Ile	Trp	Ala	Gln	Ser	Gln	Asp	Cys	Ile	Ala	Ala	Ala	Leu	Ala	Cys	Ser
				645					650					655	
Lys	Ile	Leu	Lys	Glu	Leu	Ser	Lys	Glu	Glu	Glu	Asp	Thr	Asp	Ser	Ser
			660					665					670		
Glu	Glu	Met	Leu	Ala	Leu	Ala	Glu	Glu	Tyr	Glu	His	Arg	Ala	Ile	Gly
		675					680					685			
Val	Phe	Thr	Glu	Cys	Tyr	Arg	Lys	Asp	Glu	Glu	Arg	Ala	Gln	Lys	Leu
	690					695					700				
Leu	Thr	Arg	Val	Ser	Glu	Ala	Trp	Gly	Lys	Thr	Thr	Cys	Leu	Gln	Leu
705					710					715					720
Ala	Leu	Glu	Ala	Lys	Asp	Met	Lys	Phe	Val	Ser	His	Gly	Gly	Ile	Gln
				725					730					735	
Ala	Phe	Leu	Thr	Lys	Val	Trp	Trp	Gly	Gln	Leu	Ser	Val	Asp	Asn	Gly
			740					745					750		
Leu	Trp	Arg	Val	Thr	Leu	Cys	Met	Leu	Ala	Phe	Pro	Leu	Leu	Leu	Thr
	755					760					765				
Gly	Leu	Ile	Ser	Phe	Arg	Glu	Lys	Arg	Leu	Gln	Asp	Val	Gly	Thr	Pro
770						775					780				
Ala	Ala	Arg	Ala	Arg	Ala	Phe	Phe	Thr	Ala	Pro	Val	Val	Val	Phe	His
785					790					795					800
Leu	Asn	Ile	Leu	Ser	Tyr	Phe	Ala	Phe	Leu	Cys	Leu	Phe	Ala	Tyr	Val
				805					810					815	
Leu	Met	Val	Asp	Phe	Gln	Pro	Val	Pro	Ser	Trp	Cys	Glu	Cys	Ala	Ile
			820					825					830		
Tyr	Leu	Trp	Leu	Phe	Ser	Leu	Val	Cys	Glu	Glu	Met	Arg	Gln	Leu	Phe
	835					840						845			
Tyr	Asp	Pro	Asp	Glu	Cys	Gly	Leu	Met	Lys	Lys	Ala	Ala	Leu	Tyr	Phe
850						855					860				
Ser	Asp	Phe	Trp	Asn	Lys	Leu	Asp	Val	Gly	Ala	Ile	Leu	Leu	Phe	Val
865					870					875					880
Ala	Gly	Leu	Thr	Cys	Arg	Leu	Ile	Pro	Ala	Thr	Leu	Tyr	Pro	Gly	Arg
				885					890					895	
Val	Ile	Leu	Ser	Leu	Asp	Phe	Ile	Leu	Phe	Cys	Leu	Arg	Leu	Met	His
			900					905					910		
Ile	Phe	Thr	Ile	Ser	Lys	Thr	Leu	Gly	Pro	Lys	Ile	Ile	Ile	Val	Lys
		915					920						925		

-17-

Arg Met Met Lys Asp Val Phe Phe Phe Leu Phe Leu Leu Ala Val Trp
 930 935 940
 Val Val Ser Phe Gly Val Ala Lys Gln Ala Ile Leu Ile His Asn Glu
 945 950 955 960
 Arg Arg Val Asp Trp Leu Phe Arg Gly Ala Val Tyr His Ser Tyr Leu
 965 970 975
 Thr Ile Phe Gly Gln Ile Pro Gly Tyr Ile Asp Gly Val Asn Phe Asn
 980 985 990
 Pro Glu His Cys Ser Pro Asn Gly Thr Asp Pro Tyr Lys Pro Lys Cys
 995 1000 1005
 Pro Glu Ser Asp Ala Thr Gln Gln Arg Pro Ala Phe Pro Glu Trp Leu
 1010 1015 1020
 Thr Val Leu Leu Leu Cys Leu Tyr Leu Leu Phe Thr Asn Ile Leu Leu
 1025 1030 1035 104
 Leu Asn Leu Leu Ile Ala Met Phe Asn Tyr Thr Phe Gln Gln Val Gln
 1045 1050 1055
 Glu His Thr Asp Gln Ile Trp Lys Phe Gln Arg His Asp Leu Ile Glu
 1060 1065 1070
 Glu Tyr His Gly Arg Pro Ala Ala Pro Pro Pro Phe Ile Leu Leu Ser
 1075 1080 1085
 His Leu Gln Leu Phe Ile Lys Arg Val Val Leu Lys Thr Pro Ala Lys
 1090 1095 1100
 Arg His Lys Gln Leu Lys Asn Lys Leu Glu Lys Asn Glu Glu Ala Ala
 1105 1110 1115 112
 Leu Leu Ser Trp Glu Ile Tyr Leu Lys Glu Asn Tyr Leu Gln Asn Arg
 1125 1130 1135
 Gln Phe Gln Gln Lys Gln Arg Pro Glu Gln Lys Ile Glu Asp Ile Ser
 1140 1145 1150
 Asn Lys Val Asp Ala Met Val Asp Leu Leu Asp Leu Asp Pro Leu Lys
 1155 1160 1165
 Arg Ser Gly Ser Met Glu Gln Arg Leu Ala Ser Leu Glu Glu Gln Val
 1170 1175 1180
 Ala Gln Thr Ala Arg Ala Leu His Trp Ile Val Arg Thr Leu Arg Ala
 1185 1190 1195 120
 Ser Gly Phe Ser Ser Glu Ala Asp Val Pro Thr Leu Ala Ser Gln Lys
 1205 1210 1215
 Ala Ala Glu Glu Pro Asp Ala Glu Pro Gly Gly Arg Lys Lys Thr Glu
 1220 1225 1230
 Glu Pro Gly Asp Ser Tyr His Val Asn Ala Arg His Leu Leu Tyr Pro
 1235 1240 1245
 Asn Cys Pro Val Thr Arg Phe Pro Val Pro Asn Glu Lys Val Pro Trp
 1250 1255 1260
 Glu Thr Glu Phe Leu Ile Tyr Asp Pro Pro Phe Tyr Thr Ala Glu Arg
 1265 1270 1275 128
 Lys Asp Ala Ala Ala Met Asp Pro Met Gly Asp Thr Leu Glu Pro Leu
 1285 1290 1295
 Ser Thr Ile Gln Tyr Asn Val Val Asp Gly Leu Arg Asp Arg Arg Ser
 1300 1305 1310
 Phe His Gly Pro Tyr Thr Val Gln Ala Gly Leu Pro Leu Asn Pro Met
 1315 1320 1325
 Gly Arg Thr Gly Leu Arg Gly Arg Gly Ser Leu Ser Cys Phe Gly Pro
 1330 1335 1340
 Asn His Thr Leu Tyr Pro Met Val Thr Arg Trp Arg Arg Asn Glu Asp
 1345 1350 1355 136
 Gly Ala Ile Cys Arg Lys Ser Ile Lys Lys Met Leu Glu Val Leu Val
 1365 1370 1375
 Val Lys Leu Pro Leu Ser Glu His Trp Ala Leu Pro Gly Gly Ser Arg
 1380 1385 1390
 Glu Pro Gly Glu Met Leu Pro Arg Lys Leu Lys Arg Ile Leu Arg Gln
 1395 1400 1405

-18-

Glu His Trp Pro Ser Phe Glu Asn Leu Leu Lys Cys Gly Met Glu Val
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 Tyr Lys Gly Tyr Met Asp Asp Pro Arg Asn Thr Asp Asn Ala Trp Ile
 1425 1430 1435 144
 Glu Thr Val Ala Val Ser Val His Phe Gln Asp Gln Asn Asp Val Glu
 1445 1450 1455
 Leu Asn Arg Leu Asn Ser Asn Leu His Ala Cys Asp Ser Gly Ala Ser
 1460 1465 1470
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 Lys Thr Leu Leu Gln Lys Ala Ala Ala Glu Phe Gly Ala His Tyr
 1490 1495 1500

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 <212> PRT
 <213> C. Elegans

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 Phe Phe Leu Thr Leu Ile Ala Gly Val Thr His Phe Tyr Phe Pro Glu
 50 55 60
 Lys Leu Leu Gly Lys Ser Glu Asn Leu Asp His Arg Tyr Gln Ser Ser
 65 70 75 80
 Glu Gln Lys Val Leu Ile Glu Trp Thr Glu Asn Lys Ala Val Ala Glu
 85 90 95
 Ser Leu Arg Ala Asn Ser Val Thr Val Glu Glu Asn Glu Ser Glu Arg
 100 105 110
 Glu Thr Glu Thr Gln Thr Lys Arg Arg Arg Lys Lys Gln Arg Ser Thr
 115 120 125
 Ser Ser Asp Lys Ala Pro Leu Asn Ser Ala Pro Arg His Val Gln Lys
 130 135 140
 Phe Asp Trp Lys Asp Met Leu His Leu Ala Asp Ile Ser Gly Arg Lys
 145 150 155 160
 Arg Gly Asn Ser Thr Thr Ser His Ser Gly His Ala Thr Arg Ala Gly
 165 170 175
 Ser Leu Lys Gly Lys Asn Trp Ile Glu Cys Arg Leu Lys Met Arg Gln
 180 185 190
 Cys Ser Tyr Phe Val Pro Ser Gln Arg Phe Ser Glu Arg Cys Gly Cys
 195 200 205
 Gly Lys Glu Arg Ser Lys His Thr Glu Glu Val Leu Glu Arg Ser Gln
 210 215 220
 Asn Lys Asn His Pro Leu Asn His Leu Thr Leu Pro Gly Ile His Glu
 225 230 235 240
 Val Asp Thr Thr Asp Ala Asp Ala Asp Asp Asn Glu Val Asn Leu Thr
 245 250 255
 Pro Gly Arg Trp Ser Ile Gln Ser His Thr Glu Ile Val Pro Thr Asp
 260 265 270
 Ala Tyr Gly Asn Ile Val Phe Glu Gly Thr Ala His His Ala Gln Tyr
 275 280 285
 Ala Arg Ile Ser Phe Asp Ser Asp Pro Arg Asp Ile Val His Leu Met
 290 295 300
 Met Lys Val Trp Lys Leu Lys Pro Pro Lys Leu Ile Ile Thr Ile Asn
 305 310 315 320
 Gly Gly Leu Thr Lys Phe Asp Leu Gln Pro Lys Leu Ala Arg Thr Phe

[illegible]

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Asn	Met	Asp	Phe	Thr	Phe	Arg	Tyr	Pro	Tyr	Ser	Asp	Leu	Met	Ile	Trp		
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Ala	Val	Leu	Thr	Lys	Arg	Gln	Lys	Met	Ala	Lys	Leu	Met	Trp	Thr	His		
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Gly	Glu	Glu	Gly	Met	Ala	Lys	Ala	Leu	Val	Ala	Ser	Arg	Leu	Tyr	Val		
			850						855				860				
Ser	Leu	Ala	Lys	Thr	Ala	Ser	Leu	Ala	Thr	Gly	Glu	Ile	Gly	Met	Ser		
865									870				875				
Gln	Asp	Phe	Thr	Glu	Phe	Ser	Asp	Glu	Phe	Ser	Glu	Leu	Ala	Val	Glu		
			885						890				895				
Val	Leu	Glu	Tyr	Cys	Thr	Lys	His	Gly	Arg	Asp	Gln	Thr	Leu	Arg	Leu		
			900						905				910				
Leu	Thr	Cys	Glu	Leu	Ala	Asn	Trp	Gly	Asp	Glu	Thr	Cys	Leu	Ser	Leu		
			915						920				925				
Ala	Ala	Asn	Asn	Gly	His	Arg	Lys	Phe	Leu	Ala	His	Pro	Cys	Cys	Gln		
			930						935				940				
Met	Leu	Leu	Ser	Asp	Leu	Trp	Gln	Gly	Gly	Leu	Leu	Met	Lys	Asn	Asn		
945									950				955				
Gln	Asn	Ser	Lys	Val	Leu	Thr	Cys	Leu	Ala	Ala	Pro	Pro	Leu	Ile	Phe		
			965						970				975				
Leu	Leu	Gly	Phe	Lys	Thr	Lys	Glu	Gln	Leu	Met	Leu	Gln	Pro	Lys	Thr		
			980						985				990				
Ala	Ala	Glu	His	Asp	Glu	Glu	Met	Ser	Asp	Ser	Glu	Met	Asn	Ser	Ala		
			995						1000				1005				
Glu	Asp	Thr	Asp	Thr	Ser	Ser	Asp	Ser	Ser	Ser	Asp	Ser	Asp	Asp	Ser		
			1010						1015				1020				
Asp	Glu	Glu	Asp	Ala	Lys	Leu	Arg	Ala	Gln	Ser	Leu	Ser	Ala	Asp	Gln		
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Pro	Leu	Ser	Ile	His	Arg	Leu	Val	Arg	Asp	Lys	Leu	Asn	Phe	Ser	Glu		
			1045						1050				1055				
Lys	Lys	Lys	Pro	Asp	Met	Gly	Ile	Ser	Arg	Ile	Val	Val	Ala	Pro	Pro		
			1060						1065				1070				
Ile	Val	Thr	Gly	Arg	Asn	Arg	Ala	Arg	Thr	Met	Ser	Ile	Lys	Lys	Ser		
			1075						1080				1085				
Lys	Lys	Asn	Val	Ile	Lys	Pro	Pro	Ala	Cys	Leu	Lys	Ile	Glu	Thr	Ser		
			1090						1095				1100				
Asp	Asp	Asp	Glu	Gln	Glu	Gln	Lys	Lys	Ala	Thr	Glu	Met	Cys	Lys	Ser		
1105									1110				1115				
Thr	Phe	Phe	Asp	Phe	Phe	Phe	Asp	Phe	Pro	Tyr	Ile	Asn	Arg	Thr	Gly		
			1125						1130				1135				
Lys	Arg	Gly	Ser	Val	Ala	Val	Ala	Met	Asn	His	Asp	Asp	Met	Tyr	Ile		
			1140						1145				1150				
Asp	Pro	Ser	Glu	Glu	Leu	Asp	Thr	Gln	Thr	Arg	Gln	Lys	Ser	Ser	Arg		
			1155						1160				1165				
Glu	Phe	Ser	Ser	Ser	Arg	Asn	Val	Thr	Val	Gln	Val	Tyr	Thr	Gln	Arg		
			1170						1175				1180				
Pro	Leu	Ser	Trp	Lys	Lys	Lys	Ile	Met	Glu	Phe	Tyr	Lys	Ala	Pro	Ile		
1185									1190				1195				
Thr	Thr	Tyr	Trp	Leu	Trp	Phe	Phe	Ala	Phe	Ile	Trp	Phe	Leu	Ile	Leu		
			1205						1210				1215				

[illegible]

-22-

1765 1770 1775
 Glu Asp Asp Phe Tyr Ala Asp Ser Pro Val Pro Met Pro Met Thr Pro
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 1795 1800 1805
 Gln Arg Asp Asp Ser Asp Tyr Glu
 1810 1815

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 <212> PRT
 <213> C. Elegans

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 Ala Pro Arg Asn Ser Met Cys Asn Ala Asn Thr Val His Ser Ile Ser
 35 40 45
 Ser Phe Arg Ser Asp His Leu Ser Arg Lys Ser Thr His Lys Phe Leu
 50 55 60
 Asp Asn Pro Asn Leu Phe Ala Ile Glu Leu Thr Glu Lys Leu Ser Pro
 65 70 75 80
 Pro Trp Ile Glu Asn Thr Phe Glu Lys Arg Glu Cys Ile Arg Phe Ala
 85 90 95
 Ala Leu Pro Lys Asp Pro Glu Arg Cys Gly Cys Gly Arg Pro Leu Ser
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 Ala His Thr Pro Ala Ser Thr Phe Ser Thr Leu Pro Val His Leu
 115 120 125
 Leu Glu Lys Glu Gln Gln Thr Trp Thr Ile Ala Asn Asn Thr Gln Thr
 130 135 140
 Ser Thr Thr Asp Ala Phe Gly Thr Ile Val Phe Gln Gly Gly Ala His
 145 150 155 160
 Ala His Lys Ala Gln Tyr Val Arg Leu Ser Tyr Asp Ser Glu Pro Leu
 165 170 175
 Asp Val Met Tyr Leu Met Glu Lys Val Trp Gly Leu Glu Ala Pro Arg
 180 185 190
 Leu Val Ile Thr Val His Gly Gly Met Ser Asn Phe Glu Leu Glu Glu
 195 200 205
 Arg Leu Gly Arg Leu Phe Arg Lys Gly Met Leu Lys Ala Ala Gln Thr
 210 215 220
 Thr Gly Ala Trp Ile Ile Thr Ser Gly Leu Asp Ser Gly Val Val Arg
 225 230 235 240
 His Val Ala Lys Ala Leu Asp Glu Ala Gly Ile Ser Ala Arg Met Arg
 245 250 255
 Ser Gln Ile Val Thr Ile Gly Ile Ala Pro Trp Gly Val Ile Lys Arg
 260 265 270
 Lys Glu Arg Leu Ile Arg Gln Asn Glu His Val Tyr Tyr Asp Val His
 275 280 285
 Ser Leu Ser Val Asn Ala Asn Val Gly Ile Leu Asn Asp Arg His Ser
 290 295 300
 Tyr Phe Leu Leu Ala Asp Asn Gly Thr Val Gly Arg Phe Gly Ala Asp
 305 310 315 320
 Leu His Leu Arg Gln Asn Leu Glu Asn His Ile Ala Thr Phe Gly Cys
 325 330 335
 Asn Gly Arg Lys Val Pro Val Val Cys Thr Leu Leu Glu Gly Gly Ile
 340 345 350
 Ser Ser Ile Asn Ala Ile His Asp Tyr Val Thr Met Lys Pro Asp Ile
 355 360 365

-23-

Pro Ala Ile Val Cys Asp Gly Ser Gly Arg Ala Ala Asp Ile Ile Ser
 370 375 380
 Phe Ala Ala Arg Tyr Ile Asn Ser Asp Gly Thr Phe Ala Ala Glu Val
 385 390 395 400
 Gly Glu Lys Leu Arg Asn Leu Ile Lys Met Val Phe Pro Glu Thr Asp
 405 410 415
 Gln Glu Glu Met Phe Arg Lys Ile Thr Glu Cys Val Ile Arg Asp Asp
 420 425 430
 Leu Leu Arg Ile Phe Arg Tyr Gly Gln Glu Glu Glu Asp Val Asp
 435 440 445
 Phe Val Ile Leu Ser Thr Val Leu Gln Lys Gln Asn Leu Pro Pro Asp
 450 455 460
 Glu Gln Leu Ala Leu Thr Leu Ser Trp Asn Arg Val Asp Leu Ala Lys
 465 470 475 480
 Ser Cys Leu Phe Ser Asn Gly Arg Lys Trp Ser Ser Asp Val Leu Glu
 485 490 495
 Lys Ala Met Asn Asp Ala Leu Tyr Trp Asp Arg Val Asp Phe Val Glu
 500 505 510
 Cys Leu Leu Glu Asn Gly Val Ser Met Lys Asn Phe Leu Ser Ile Asn
 515 520 525
 Arg Leu Glu Asn Leu Tyr Asn Met Asp Asp Ile Asn Ser Ala His Ser
 530 535 540
 Val Arg Asn Trp Met Glu Asn Phe Asp Ser Met Asp Pro His Thr Tyr
 545 550 555 560
 Leu Thr Ile Pro Met Ile Gly Gln Val Val Glu Lys Leu Met Gly Asn
 565 570 575
 Ala Phe Gln Leu Tyr Tyr Thr Ser Arg Ser Phe Lys Gly Lys Tyr Asp
 580 585 590
 Arg Tyr Lys Arg Ile Asn Gln Ser Ser Tyr Phe His Arg Lys Arg Lys
 595 600 605
 Ile Val Gln Lys Glu Leu Phe Lys Lys Lys Ser Asp Asp Gln Ile Asn
 610 615 620
 Asp Asn Glu Glu Glu Asp Phe Ser Phe Ala Tyr Pro Phe Asn Asp Leu
 625 630 635 640
 Leu Ile Trp Ala Val Leu Thr Ser Arg His Gly Met Ala Glu Cys Met
 645 650 655
 Trp Val His Gly Glu Asp Ala Met Ala Lys Cys Leu Leu Ala Ile Arg
 660 665 670
 Leu Tyr Lys Ala Thr Ala Lys Ile Ala Glu Asp Glu Tyr Leu Asp Val
 675 680 685
 Glu Glu Ala Lys Arg Leu Phe Asp Asn Ala Val Lys Cys Arg Glu Asp
 690 695 700
 Ala Ile Glu Leu Leu Asp Gln Cys Tyr Arg Ala Asp His Asp Arg Thr
 705 710 715 720
 Leu Arg Leu Leu Arg Met Glu Leu Pro His Trp Gly Asn Asn Asn Cys
 725 730 735
 Leu Ser Leu Ala Val Leu Ala Asn Thr Lys Thr Phe Leu Ala His Pro
 740 745 750
 Cys Cys Gln Ile Leu Leu Ala Glu Leu Trp His Gly Ser Leu Lys Val
 755 760 765
 Arg Ser Gly Ser Asn Val Arg Val Leu Thr Ala Leu Ile Cys Pro Pro
 770 775 780
 Ala Ile Leu Phe Met Ala Tyr Lys Pro Lys His Ser Lys Thr Ala Arg
 785 790 795 800
 Leu Leu Ser Glu Glu Thr Pro Glu Gln Leu Pro Tyr Pro Arg Glu Ser
 805 810 815
 Ile Thr Ser Thr Thr Ser Asn Arg Tyr Arg Tyr Ser Lys Gly Pro Glu
 820 825 830
 Glu Gln Lys Glu Thr Leu Leu Glu Lys Gly Ser Tyr Thr Lys Lys Val
 835 840 845

-24-

Thr	Ile	Ile	Ser	Ser	Arg	Lys	Asn	Ser	Gly	Val	Ala	Ser	Val	Tyr	Gly
850						855					860				
Ser	Ala	Ser	Ser	Met	Met	Phe	Lys	Arg	Glu	Pro	Gln	Leu	Asn	Lys	Phe
865					870					875					880
Glu	Arg	Phe	Arg	Ala	Phe	Tyr	Ser	Ser	Pro	Ile	Thr	Lys	Phe	Trp	Ser
				885					890						895
Trp	Cys	Ile	Ala	Phe	Leu	Ile	Phe	Leu	Thr	Thr	Gln	Thr	Cys	Ile	Leu
			900					905					910		
Leu	Leu	Glu	Thr	Ser	Leu	Lys	Pro	Ser	Lys	Tyr	Glu	Trp	Ile	Thr	Phe
		915					920					925			
Ile	Tyr	Thr	Val	Thr	Leu	Ser	Val	Glu	His	Ile	Arg	Lys	Leu	Met	Thr
930						935					940				
Ser	Glu	Gly	Ser	Arg	Ile	Asn	Glu	Lys	Val	Lys	Val	Phe	Tyr	Ala	Lys
945					950					955					960
Trp	Tyr	Asn	Ile	Trp	Thr	Ser	Ala	Ala	Leu	Leu	Phe	Phe	Leu	Val	Gly
				965					970						975
Tyr	Gly	Phe	Arg	Leu	Val	Pro	Met	Tyr	Arg	His	Ser	Trp	Gly	Arg	Val
			980					985					990		
Leu	Leu	Ser	Phe	Ser	Asn	Val	Leu	Phe	Tyr	Met	Lys	Ile	Phe	Glu	Tyr
		995					1000					1005			
Leu	Ser	Val	His	Pro	Leu	Leu	Gly	Pro	Tyr	Ile	Gln	Met	Ala	Ala	Lys
1010						1015					1020				
Met	Val	Trp	Ser	Met	Cys	Tyr	Ile	Cys	Val	Leu	Leu	Leu	Val	Pro	Leu
1025					1030					1035					104
Met	Ala	Phe	Gly	Val	Asn	Arg	Gln	Ala	Leu	Thr	Glu	Pro	Asn	Val	Lys
				1045						1050					1055
Asp	Trp	His	Trp	Leu	Leu	Val	Arg	Asn	Ile	Phe	Tyr	Lys	Pro	Tyr	Phe
			1060					1065					1070		
Met	Leu	Tyr	Gly	Glu	Val	Tyr	Ala	Gly	Glu	Ile	Asp	Thr	Cys	Gly	Asp
		1075					1080					1085			
Glu	Gly	Ile	Arg	Cys	Phe	Pro	Gly	Tyr	Phe	Ile	Pro	Pro	Leu	Leu	Met
1090						1095					1100				
Val	Ile	Phe	Leu	Leu	Val	Ala	Asn	Ile	Leu	Leu	Leu	Asn	Leu	Leu	Ile
1105					1110						1115				112
Ala	Ile	Phe	Asn	Asn	Ile	Tyr	Asn	Asp	Ser	Ile	Glu	Lys	Ser	Lys	Glu
				1125						1130					1135
Ile	Trp	Leu	Phe	Gln	Arg	Tyr	Gln	Gln	Leu	Met	Glu	Tyr	His	Asp	Ser
			1140					1145					1150		
Pro	Phe	Leu	Pro	Pro	Pro	Phe	Ser	Ile	Phe	Ala	His	Val	Tyr	His	Phe
		1155					1160					1165			
Ile	Asp	Tyr	Leu	Tyr	Asn	Leu	Arg	Arg	Pro	Asp	Thr	Lys	Arg	Phe	Arg
1170					1175						1180				
Ser	Glu	His	Ser	Ile	Lys	Leu	Ser	Val	Thr	Glu	Asp	Glu	Met	Lys	Arg
1185					1190					1195					120
Ile	Gln	Asp	Phe	Glu	Glu	Asp	Cys	Ile	Asp	Thr	Leu	Thr	Arg	Ile	Arg
			1205						1210					1215	
Lys	Leu	Lys	Leu	Asn	Thr	Lys	Glu	Pro	Leu	Ser	Val	Thr	Asp	Leu	Thr
			1220					1225					1230		
Glu	Leu	Thr	Cys	Gln	Arg	Val	His	Asp	Leu	Met	Gln	Glu	Asn	Phe	Leu
		1235					1240					1245			
Leu	Lys	Ser	Arg	Val	Tyr	Asp	Ile	Glu	Thr	Lys	Ile	Asp	His	Ile	Ser
1250						1255					1260				
Asn	Ser	Ser	Asp	Glu	Val	Val	Gln	Ile	Leu	Lys	Asn	Lys	Lys	Leu	Ser
1265					1270					1275					128
Gln	Asn	Phe	Ala	Ala	Ser	Ser	Leu	Ser	Leu	Pro	Asp	Thr	Ser	Ile	Glu
				1285						1290					1295
Val	Pro	Lys	Ile	Thr	Lys	Thr	Leu	Ile	Asp	Cys	His	Leu	Ser	Pro	Val
			1300					1305					1310		
Ser	Ile	Glu	Asp	Arg	Leu	Ala	Thr	Arg	Ser	Pro	Leu	Leu	Ala	Asn	Leu
		1315					1320						1325		

-25-

Gln Arg Asp His Thr Leu Arg Lys Leu Pro Thr Trp Glu Thr Ser Thr
 1330 1335 1340
 Ala Ser Thr Ser Ser Phe Glu Phe Val Phe Tyr Phe Thr Arg His Glu
 1345 1350 1355 136
 Gly Asn Glu Asn Lys Tyr Glu Phe Lys Lys Leu Glu Lys Gly Gly Phe
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 Trp Arg Asn Asn Tyr Val Ile Ser Trp Arg Leu
 1380 1385

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 Trp Cys Thr Met Glu Ser Asp Glu Leu Gly Val Thr Arg Tyr Leu Gln
 20 25 30
 Ser Lys Gly Gly Asp Gln Val Pro Pro Thr Ser Thr Thr Gly Gly
 35 40 45
 Ala Gly Gly Asp Gly Asn Ala Val Pro Thr Thr Ser Gln Ala Gln Ala
 50 55 60
 Gln Thr Phe Asn Ser Gly Arg Gln Thr Thr Gly Met Ser Ser Gly Asp
 65 70 75 80
 Arg Leu Asn Glu Asp Val Ser Ala Thr Ala Asn Ser Ala Gln Leu Val
 85 90 95
 Leu Pro Thr Pro Leu Phe Asn Gln Met Arg Phe Thr Glu Ser Asn Met
 100 105 110
 Ser Leu Asn Arg His Asn Trp Val Arg Glu Thr Phe Thr Arg Arg Glu
 115 120 125
 Cys Ser Arg Phe Ile Ala Ser Ser Arg Asp Leu His Lys Cys Gly Cys
 130 135 140
 Gly Arg Thr Arg Asp Ala His Arg Asn Ile Pro Glu Leu Thr Ser Glu
 145 150 155 160
 Phe Leu Arg Gln Lys Arg Ser Val Ala Ala Leu Glu Gln Gln Arg Ser
 165 170 175
 Ile Ser Asn Val Asn Asp Asp Ile Asn Thr Gln Asn Met Tyr Thr Lys
 180 185 190
 Arg Gly Ala Asn Glu Lys Trp Ser Leu Arg Lys His Thr Val Ser Leu
 195 200 205
 Ala Thr Asn Ala Phe Gly Gln Val Glu Phe Gln Gly Gly Pro His Pro
 210 215 220
 Tyr Lys Ala Gln Tyr Val Arg Val Asn Phe Asp Thr Glu Pro Ala Tyr
 225 230 235 240
 Ile Met Ser Leu Phe Glu His Val Trp Gln Ile Ser Pro Pro Arg Leu
 245 250 255
 Ile Ile Thr Val His Gly Gly Thr Ser Asn Phe Asp Leu Gln Pro Lys
 260 265 270
 Leu Ala Arg Val Phe Arg Lys Gly Leu Leu Lys Ala Ala Ser Thr Thr
 275 280 285
 Gly Ala Trp Ile Ile Thr Ser Gly Cys Asp Thr Gly Val Val Lys His
 290 295 300
 Val Ala Ala Ala Leu Glu Gly Ala Gln Ser Ala Gln Arg Asn Lys Ile
 305 310 315 320
 Val Cys Ile Gly Ile Ala Pro Trp Gly Leu Leu Lys Lys Arg Glu Asp
 325 330 335
 Phe Ile Gly Gln Asp Lys Thr Val Pro Tyr Tyr Pro Ser Ser Ser Lys
 340 345 350
 Gly Arg Phe Thr Gly Leu Asn Asn Arg His Ser Tyr Phe Leu Leu Val

355					360					365					
Asp	Asn	Gly	Thr	Val	Gly	Arg	Tyr	Gly	Ala	Glu	Val	Ile	Leu	Arg	Lys
370					375					380					
Arg	Leu	Glu	Met	Tyr	Ile	Ser	Gln	Lys	Gln	Lys	Ile	Phe	Gly	Gly	Thr
385					390					395					
Arg	Ser	Val	Pro	Val	Val	Cys	Val	Val	Leu	Glu	Gly	Gly	Ser	Cys	Thr
405					410					415					
Ile	Arg	Ser	Val	Leu	Asp	Tyr	Val	Thr	Asn	Val	Pro	Arg	Val	Pro	Val
420					425					430					
Val	Val	Cys	Asp	Gly	Ser	Gly	Arg	Ala	Ala	Asp	Leu	Leu	Ala	Phe	Ala
435					440					445					
His	Gln	Asn	Val	Thr	Glu	Asp	Gly	Leu	Leu	Pro	Asp	Asp	Ile	Arg	Arg
450					455					460					
Gln	Val	Leu	Leu	Leu	Val	Glu	Thr	Thr	Phe	Gly	Cys	Ser	Glu	Ala	Ala
465					470					475					
Ala	His	Arg	Leu	Leu	His	Glu	Leu	Thr	Val	Cys	Ala	Gln	His	Lys	Asn
485					490					495					
Leu	Leu	Thr	Ile	Phe	Arg	Leu	Gly	Glu	Gln	Gly	Glu	His	Asp	Val	Asp
500					505					510					
His	Ala	Ile	Leu	Thr	Ala	Leu	Leu	Lys	Gly	Gln	Asn	Leu	Ser	Ala	Ala
515					520					525					
Asp	Gln	Leu	Ala	Leu	Ala	Leu	Ala	Trp	Asn	Arg	Val	Asp	Ile	Ala	Arg
530					535					540					
Ser	Asp	Val	Phe	Ala	Met	Gly	His	Glu	Trp	Pro	Gln	Ala	Ala	Leu	His
545					550					555					
Asn	Ala	Met	Met	Glu	Ala	Leu	Ile	His	Asp	Arg	Val	Asp	Phe	Val	Arg
565					570					575					
Leu	Leu	Leu	Glu	Gln	Gly	Ile	Asn	Met	Gln	Lys	Phe	Leu	Thr	Ile	Ser
580					585					590					
Arg	Leu	Asp	Glu	Leu	Tyr	Asn	Thr	Asp	Lys	Gly	Pro	Pro	Asn	Thr	Leu
595					600					605					
Phe	Tyr	Ile	Val	Arg	Asp	Val	Val	Arg	Val	Arg	Gln	Gly	Tyr	Arg	Phe
610					615					620					
Lys	Leu	Pro	Asp	Ile	Gly	Leu	Val	Ile	Glu	Lys	Leu	Met	Gly	Asn	Ser
625					630					635					
Tyr	Gln	Cys	Ser	Tyr	Thr	Thr	Ser	Glu	Phe	Arg	Asp	Lys	Tyr	Lys	Gln
645					650					655					
Arg	Met	Lys	Arg	Val	Lys	His	Ala	Gln	Lys	Lys	Ala	Met	Gly	Val	Phe
660					665					670					
Ser	Ser	Arg	Pro	Ser	Arg	Thr	Gly	Ser	Gly	Ile	Ala	Ser	Arg	Gln	Ser
675					680					685					
Thr	Glu	Gly	Met	Gly	Gly	Val	Gly	Gly	Gly	Ser	Ser	Val	Ala	Gly	Val
690					695					700					
Phe	Gly	Asn	Ser	Phe	Gly	Asn	Gln	Asp	Pro	Pro	Leu	Asp	Pro	His	Val
705					710					715					
Asn	Arg	Ser	Ala	Leu	Ser	Gly	Ser	Arg	Ala	Leu	Ser	Asn	His	Ile	Leu
725					730					735					
Trp	Arg	Ser	Ala	Phe	Arg	Gly	Asn	Phe	Pro	Ala	Asn	Pro	Met	Arg	Pro
740					745					750					
Pro	Asn	Leu	Gly	Asp	Ser	Arg	Asp	Cys	Gly	Ser	Glu	Phe	Asp	Glu	Glu
755					760					765					
Leu	Ser	Leu	Thr	Ser	Ala	Ser	Asp	Gly	Ser	Gln	Thr	Glu	Pro	Asp	Phe
770					775					780					
Arg	Tyr	Pro	Tyr	Ser	Glu	Leu	Met	Ile	Trp	Ala	Val	Leu	Thr	Lys	Arg
785					790					795					
Gln	Asp	Met	Ala	Met	Cys	Met	Trp	Gln	His	Gly	Glu	Glu	Ala	Met	Ala
805					810					815					
Lys	Ala	Leu	Val	Ala	Cys	Arg	Leu	Tyr	Lys	Ser	Leu	Ala	Thr	Glu	Ala
820					825					830					
Ala	Glu	Asp	Tyr	Leu	Glu	Val	Glu	Ile	Cys	Glu	Glu	Leu	Lys	Lys	Tyr

-27-

835	840	845
Ala Glu Phe Arg Ile Leu Ser Leu Glu Leu Leu Asp His Cys Tyr		
850	855	860
His Val Asp Asp Ala Gln Thr Leu Gln Leu Leu Thr Tyr Glu Leu Ser		
865	870	875
Asn Trp Ser Asn Glu Thr Cys Leu Ala Leu Ala Val Ile Val Asn Asn		
885	890	895
Lys His Phe Leu Ala His Pro Cys Cys Gln Ile Leu Leu Ala Asp Leu		
900	905	910
Trp His Gly Gly Leu Arg Met Arg Thr His Ser Asn Ile Lys Val Val		
915	920	925
Leu Gly Leu Ile Cys Pro Pro Phe Ile Gln Met Leu Glu Phe Lys Thr		
930	935	940
Arg Glu Glu Leu Leu Asn Gln Pro Gln Thr Ala Ala Glu His Gln Asn		
945	950	955
Asp Met Asn Tyr Ser Ser Ser Ser Ser Ser Ser Ser Ser Ser Ser		
965	970	975
Ser Ser Ser Ser Ser Asp Ser Ser Ser Phe Glu Asp Asp Asp Asp Glu		
980	985	990
Asn Asn Ala His Asn His Asp Gln Lys Arg Thr Arg Lys Thr Ser Gln		
995	1000	1005
Gly Ser Ala Gln Ser Leu Asn Ile Thr Ser Leu Phe His Ser Arg Arg		
1010	1015	1020
Arg Lys Ala Lys Lys Asn Glu Lys Cys Asp Arg Glu Thr Asp Ala Ser		
1025	1030	1035
Ala Cys Glu Ala Gly Asn Arg Gln Ile Gln Asn Gly Gly Leu Thr Ala		
1045	1050	1055
Glu Tyr Gly Thr Phe Gly Glu Ser Asn Gly Val Ser Pro Pro Pro Pro		
1060	1065	1070
Tyr Met Arg Ala Asn Ser Arg Ser Arg Tyr Asn Asn Arg Ser Asp Met		
1075	1080	1085
Ser Lys Thr Ser Ser Val Ile Phe Gly Ser Asp Pro Asn Leu Ser Lys		
1090	1095	1100
Leu Gln Lys Ser Asn Ile Thr Ser Thr Asp Arg Pro Asn Pro Met Glu		
1105	1110	1115
Gln Phe Gln Gly Thr Arg Lys Ile Lys Met Arg Arg Arg Phe Tyr Glu		
1125	1130	1135
Phe Tyr Ser Ala Pro Ile Ser Thr Phe Trp Ser Trp Thr Ile Ser Phe		
1140	1145	1150
Ile Leu Phe Ile Thr Phe Phe Thr Tyr Thr Leu Leu Val Lys Thr Pro		
1155	1160	1165
Pro Arg Pro Thr Val Ile Glu Tyr Ile Leu Ile Ala Tyr Val Ala Ala		
1170	1175	1180
Phe Gly Leu Glu Gln Val Arg Lys Ile Ile Met Ser Asp Ala Lys Pro		
1185	1190	1195
Phe Tyr Glu Lys Ile Arg Thr Tyr Val Cys Ser Phe Trp Asn Cys Val		
1205	1210	1215
Thr Ile Leu Ala Ile Ile Phe Tyr Ile Val Gly Phe Phe Met Arg Cys		
1220	1225	1230
Phe Gly Ser Val Ala Tyr Gly Arg Val Ile Leu Ala Cys Asp Ser Val		
1235	1240	1245
Leu Trp Thr Met Lys Leu Leu Asp Tyr Met Ser Val His Pro Lys Leu		
1250	1255	1260
Gly Pro Tyr Val Thr Met Ala Gly Lys Met Ile Gln Asn Met Ser Tyr		
1265	1270	1275
Ile Ile Val Met Leu Val Val Thr Leu Leu Ser Phe Gly Leu Ala Arg		
1285	1290	1295
Gln Ser Ile Thr Tyr Pro Asp Glu Thr Trp His Trp Ile Leu Val Arg		
1300	1305	1310
Asn Ile Phe Leu Lys Pro Tyr Phe Met Leu Tyr Gly Glu Val Tyr Ala		

-28-

1315	1320	1325
Asp Glu Ile Asp Thr Cys Gly Asp Glu Ala Trp Asp Gln His Leu Glu		
1330	1335	1340
Asn Gly Gly Pro Val Ile Leu Gly Asn Gly Thr Thr Gly Leu Ser Cys		
1345	1350	1355
Val Pro Gly Tyr Trp Ile Pro Pro Leu Leu Met Thr Phe Phe Leu Leu		
1365	1370	1375
Ile Ala Asn Ile Leu Leu Met Ser Met Leu Ile Ala Ile Phe Asn His		
1380	1385	1390
Ile Phe Asp Ala Thr Asp Glu Met Ser Gln Gln Ile Trp Leu Phe Gln		
1395	1400	1405
Arg Tyr Lys Gln Val Met Glu Tyr Glu Ser Thr Pro Phe Leu Pro Pro		
1410	1415	1420
Pro Leu Thr Pro Leu Tyr His Gly Val Leu Ile Leu Gln Phe Val Arg		
1425	1430	1435
Thr Arg Leu Ser Cys Ser Lys Ser Gln Glu Arg Asn Pro Ile Leu Leu		
1445	1450	1455
Leu Lys Ile Ala Glu Leu Phe Leu Asp Asn Asp Gln Ile Glu Lys Leu		
1460	1465	1470
His Asp Phe Glu Glu Asp Cys Met Glu Asp Leu Ala Arg Gln Lys Leu		
1475	1480	1485
Asn Glu Lys Asn Thr Ser Asn Glu Gln Arg Ile Leu Arg Ala Asp Ile		
1490	1495	1500
Arg Thr Asp Gln Ile Leu Asn Arg Leu Ile Asp Leu Gln Ala Lys Glu		
1505	1510	1515
Ser Met Gly Arg Asp Val Ile Asn Asp Val Glu Ser Arg Leu Ala Ser		
1525	1530	1535
Val Glu Lys Ala Gln Asn Glu Ile Leu Glu Cys Val Arg Ala Leu Leu		
1540	1545	1550
Asn Gln Asn Asn Ala Pro Thr Ala Ile Gly Arg Cys Phe Ser Pro Ser		
1555	1560	1565
Pro Asp Pro Leu Val Glu Thr Ala Asn Gly Thr Pro Gly Pro Leu Leu		
1570	1575	1580
Leu Lys Leu Pro Gly Thr Asp Pro Ile Leu Glu Glu Lys Asp His Asp		
1585	1590	1595
Ser Gly Glu Asn Ser Asn Ser Leu Pro Pro Gly Arg Ile Arg Arg Asn		
1605	1610	1615
Arg Thr Ala Thr Ile Cys Gly Gly Tyr Val Ser Glu Glu Arg Asn Met		
1620	1625	1630
Met Leu Leu Ser Pro Lys Pro Ser Asp Val Ser Gly Ile Pro Gln Gln		
1635	1640	1645
Arg Leu Met Ser Val Thr Ser Met Asp Pro Leu Pro Leu Pro Leu Ala		
1650	1655	1660
Lys Leu Ser Thr Met Ser Ile Arg Arg Arg His Glu Glu Tyr Thr Ser		
1665	1670	1675
Ile Thr Asp Ser Ile Ala Ile Arg His Pro Glu Arg Arg Ile Arg Asn		
1685	1690	1695
Asn Arg Ser Asn Ser Ser Glu His Asp Glu Ser Ala Val Asp Ser Glu		
1700	1705	1710
Gly Gly Gly Asn Val Thr Ser Ser Pro Arg Lys Arg Ser Thr Arg Asp		
1715	1720	1725
Leu Arg Met Thr Pro Ser Ser Gln Val Glu Glu Ser Thr Ser Arg Asp		
1730	1735	1740
Gln Ile Phe Glu Ile Asp His Pro Glu His Glu Glu Asp Glu Ala Gln		
1745	1750	1755
Ala Asp Cys Glu Leu Thr Asp Val Ile Thr Glu Glu Glu Asp Glu Glu		
1765	1770	1775
Glu Asp Asp Glu Glu Asp Asp Ser His Glu Arg His His Ile His Pro		
1780	1785	1790
Arg Arg Lys Ser Ser Arg Gln Asn Arg Gln Pro Ser His Thr Leu Glu		

-29-

1795	1800	1805
Thr Asp Leu Ser Glu Gly Glu Glu Val Asp Pro Leu Asp Val Leu Lys		
1810	1815	1820
Met Lys Glu Leu Pro Ile Ile His Gln Ile Leu Asn Glu Glu Glu Gln		
1825	1830	1835
Ala Gly Ala Pro His Ser Thr Pro Val Ile Ala Ser Pro Ser Ser Ser		
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Arg Ala Asp Leu Thr Ser Gln Lys Cys Ser Asp Val		1855
	1860	1865

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 <213> Mus Musculus

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ggctgcaggc cgcgagggtg gaggaggagc cgctgccctt ccggagtcgg ccccgtaggg	180
agaatgtccc agaaatcctg gatagagagc actttgacca agagggagtg tgtatatatt	240
ataccaagct ccaaagacct tcacagatgt cttccaggat gtcagatttg tcagcaactt	300
gtcagatgtt tctgtggtcg tttggtcaag caacatgcat gctttactgc aagtcttgcc	360
atgaaatact cagatgtgaa attgggtgaa cactttaacc aggcaataga agaatggtct	420
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ggttctcat	489

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Val Tyr Ile Ile Pro Ser Ser Lys Asp Pro His Arg Cys Leu Pro Gly	
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Cys Gln Ile Cys Gln Gln Leu Val Arg Cys Phe Cys Gly Arg Leu Val	
35 40 45	
Lys Gln His Ala Cys Phe Thr Ala Ser Leu Ala Met Lys Tyr Ser Asp	
50 55 60	
Val Lys Leu Gly Glu His Phe Asn Gln Ala Ile Glu Glu Trp Ser Val	
65 70 75 80	
Glu Lys His Thr Glu Gln Ser Pro Thr Asp Ala Tyr Gly Val Ile Asn	
85 90 95	
Phe Gln Gly Gly Ser His	
100	

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 <212> DNA
 <213> Homo Sapiens

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-30-

<222> (89)...(89)

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<400> 18

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ctagtggctc	tcacctgctt	cctcctgggc	gtgggctgcc	ggctgacccc	gggtttgtac	180
cacctggggc	gcactgtcct	ctgcatcgac	ttcatggttt	tcacgggtgcg	gctgcttcac	240
atcttcacgg	tcaacaaaca	gctggggccc	aagatcgta	tcgtgagcaa	gatgatgaag	300
gacgtgttct	tcttcctctt	cttcctcggc	gtgtggctgg	tagctatggg	ttggggccacg	360
gaggggttcc	tgaggccacg	ggacagtgac	ttcccaagta	tcctgncgcc		410

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<212> PRT

<213> Homo Sapiens

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<222> (15)...(15)

<223> UNKNOWN

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<223> UNKNOWN

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<222> (131)...(131)

<223> UNKNOWN

<400> 19

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Cys	Leu	Thr	Glu	Pro	Ala	Pro	Ala	Xaa	Tyr	Leu	Ala	Asp	Ser	Trp	Asn
			20					25				30			
Gln	Cys	Asp	Leu	Val	Ala	Leu	Thr	Cys	Phe	Leu	Leu	Gly	Val	Gly	Cys
		35					40					45			
Arg	Leu	Thr	Pro	Gly	Leu	Tyr	His	Leu	Gly	Arg	Thr	Val	Leu	Cys	Ile
	50					55					60				
Asp	Phe	Met	Val	Phe	Thr	Val	Arg	Leu	Leu	His	Ile	Phe	Thr	Val	Asn
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<211> 389

<212> DNA

<213> Homo Sapiens

<400> 20

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-31-

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 <213> Homo Sapiens

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tgttactaa	cctctttccc	cactgaaata	acttttttca	ataacatgat	tttaacaaca	360
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-32-

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-33-

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 35 40 45
 Ala Val Glu Leu Leu Glu Gln Ser Phe Arg Gln Asp Glu Thr Met Ala
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 Met Lys Leu Leu Thr Tyr Glu Leu Lys Asn Trp Ser Asn Ser Thr Cys
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 Leu Lys Leu Ala Val Ser Ser Arg Leu Arg Pro Phe Val Ala His Thr
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-34-

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Val	Arg	Ile	Leu	Asp	Ser	Asn	Glu	Gly	Lys	Asn	Glu	Met	Glu	Ile	Gln
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Met	Lys	Ser	Lys	Lys	Leu	Pro	Ile	Thr	Arg	Lys	Phe	Tyr	Ala	Phe	Tyr
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His	Ala	Pro	Ile	Val	Lys	Phe	Trp	Phe	Asn	Thr	Leu	Ala	Tyr	Leu	Gly
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225					230					235					240
Pro	Ser	Val	Gln	Glu	Trp	Ile	Val	Ile	Ala	Tyr	Ile	Phe	Thr	Tyr	Ala
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Asp	Phe	Leu	Ala	Val	Asn	Gln	Gln	Ala	Gly	Pro	Tyr	Val	Met	Met	Ile
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Glu	Arg	Val	Glu	Gln	Met	Cys	Ile	Gln	Ile	Lys	Glu	Val	Gly	Asp	Arg
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-35-

Val	Asn	Tyr	Ile	Lys	Arg	Ser	Leu	Gln	Ser	Leu	Asp	Ser	Gln	Ile	Gly	580	585	590
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Thr	Ala	Gln	Lys	Ala	Ser	Glu	Ala	Ser	Lys	Val	His	Asn	Glu	Ile	Thr	610	615	620
Arg	Glu	Leu	Ser	Ile	Ser	Lys	His	Leu	Ala	Gln	Asn	Leu	Ile	Asp	Asp	625	630	635
Gly	Pro	Val	Arg	Pro	Ser	Val	Trp	Lys	Lys	His	Gly	Val	Val	Asn	Thr	645	650	655
Leu	Ser	Ser	Ser	Leu	Pro	Gln	Gly	Asp	Leu	Glu	Ser	Asn	Asn	Pro	Phe	660	665	670
His	Cys	Asn	Ile	Leu	Met	Lys	Asp	Asp	Lys	Asp	Pro	Gln	Cys	Asn	Ile	675	680	685
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Ser	Cys	Lys	Ser	His	Leu	Glu	Thr	Gly	Thr	Lys	Asp	Gln	Glu	Thr	Val	770	775	780
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Ser	Glu	His	Asp	Ile	Leu	Lys	Ser	Gly	His	Leu	Tyr	Ile	Ile	Lys	Ser	995	1000	1005
Phe	Leu	Pro	Glu	Val	Val	Asn	Thr	Trp	Ser	Ser	Ile	Tyr	Lys	Glu	Asp	1010	1015	1020
Thr	Val	Leu	His	Leu	Cys	Leu	Arg	Glu	Ile	Gln	Gln	Gln	Arg	Ala	Ala	1025	1030	1035
Gln	Lys	Leu	Thr	Phe	Ala	Phe	Asn	Gln	Met	Lys	Pro	Lys	Ser	Ile	Pro	1045	1050	1055

-36-

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 1075 1080 1085
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 Glu Ile Met Leu Ala Phe Ser His Trp Thr Tyr Glu Tyr Thr Arg Gly
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 Glu Leu Leu Val Leu Asp Leu Gln Gly Val Gly Glu Asn Leu Thr Asp
 1125 1130 1135
 Pro Ser Val Ile Lys Ala Glu Glu Lys Arg Ser Cys Asp Met Val Phe
 1140 1145 1150
 Gly Pro Ala Asn Leu Gly Glu Asp Ala Ile Lys Asn Phe Arg Ala Lys
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 His His Cys Asn Ser Cys Cys Arg Lys Leu Lys Leu Pro Asp Leu Lys
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-38-

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tgtaatthar	cagccccaga	tattgttgaa	tattcaacaa	taacaagaaa	agcttttcat	7080
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-41-

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ctcatagata	cagacaaggc	aagagatgat	aagctgttta	aatagtgttt	aatattgatt	7260
gggggtgggg	agaaagaaaa	agtgtattac	ttaaagatac	tatatacskt	ttktatatca	7320
ttaaattcttt	aaaagaaatn	naataaattt	attgttttnc	aaaaaaaaac	ccnntaaaaa	7380
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<211> 1865

<212> PRT

<213> Homo Sapiens

<400> 28

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			20					25					30		
Cys	Gln	Ile	Cys	Gln	Gln	Leu	Val	Arg	Cys	Phe	Cys	Gly	Arg	Leu	Val
		35				40						45			
Lys	Gln	His	Ala	Cys	Phe	Thr	Ala	Ser	Leu	Ala	Met	Lys	Tyr	Ser	Asp
		50				55					60				
Val	Lys	Leu	Gly	Asp	His	Phe	Asn	Gln	Ala	Ile	Glu	Glu	Trp	Ser	Val
65					70					75				80	
Glu	Lys	His	Thr	Glu	Gln	Ser	Pro	Thr	Asp	Ala	Tyr	Gly	Val	Ile	Asn
				85					90					95	
Phe	Gln	Gly	Gly	Ser	His	Ser	Tyr	Arg	Ala	Lys	Tyr	Val	Arg	Leu	Ser
			100					105					110		
Tyr	Asp	Thr	Lys	Pro	Glu	Val	Ile	Leu	Gln	Leu	Leu	Leu	Lys	Glu	Trp
		115					120					125			
Gln	Met	Glu	Leu	Pro	Lys	Leu	Val	Ile	Ser	Val	His	Gly	Gly	Met	Gln
		130					135					140			
Lys	Phe	Glu	Leu	His	Pro	Arg	Ile	Lys	Gln	Leu	Leu	Gly	Lys	Gly	Leu
145					150					155					160
Ile	Lys	Ala	Ala	Val	Thr	Thr	Gly	Ala	Trp	Ile	Leu	Thr	Gly	Gly	Val
				165					170					175	
Asn	Thr	Gly	Val	Ala	Lys	His	Val	Gly	Asp	Ala	Leu	Lys	Glu	His	Ala
			180					185					190		
Ser	Arg	Ser	Ser	Arg	Lys	Ile	Cys	Thr	Ile	Gly	Ile	Ala	Pro	Trp	Gly
		195					200					205			
Val	Ile	Glu	Asn	Arg	Asn	Asp	Leu	Val	Gly	Arg	Asp	Val	Val	Ala	Pro
		210				215					220				
Tyr	Gln	Thr	Leu	Leu	Asn	Pro	Leu	Ser	Lys	Leu	Asn	Val	Leu	Asn	Asn
225					230					235				240	
Leu	His	Ser	His	Phe	Ile	Leu	Val	Asp	Asp	Gly	Thr	Val	Gly	Lys	Tyr
				245					250					255	
Gly	Ala	Glu	Val	Arg	Leu	Arg	Arg	Glu	Leu	Glu	Lys	Thr	Ile	Asn	Gln
			260					265					270		
Gln	Arg	Ile	His	Ala	Arg	Ile	Gly	Gln	Gly	Val	Pro	Val	Val	Ala	Leu
		275					280						285		
Ile	Phe	Glu	Gly	Gly	Pro	Asn	Val	Ile	Leu	Thr	Val	Leu	Glu	Tyr	Leu
		290				295					300				
Gln	Glu	Ser	Pro	Pro	Val	Pro	Val	Val	Val	Cys	Glu	Gly	Thr	Gly	Arg
305					310					315				320	
Ala	Ala	Asp	Leu	Leu	Ala	Tyr	Ile	His	Lys	Gln	Thr	Glu	Glu	Gly	Gly
				325					330					335	
Asn	Leu	Pro	Asp	Ala	Ala	Glu	Pro	Asp	Ile	Ile	Ser	Thr	Ile	Lys	Lys
			340					345					350		
Thr	Phe	Asn	Phe	Gly	Gln	Asn	Glu	Ala	Leu	His	Leu	Phe	Gln	Thr	Leu
		355					360						365		

-42-

Met	Glu	Cys	Met	Lys	Arg	Lys	Glu	Leu	Ile	Thr	Val	Phe	His	Ile	Gly
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Ser	Asp	Glu	His	Gln	Asp	Ile	Asp	Val	Ala	Ile	Leu	Thr	Ala	Leu	Leu
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Lys	Gly	Thr	Asn	Ala	Ser	Ala	Phe	Asp	Gln	Leu	Ile	Leu	Thr	Leu	Ala
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Trp	Asp	Arg	Val	Asp	Ile	Ala	Lys	Asn	His	Val	Phe	Val	Tyr	Gly	Gln
			420					425					430		
Gln	Trp	Leu	Val	Gly	Ser	Leu	Glu	Gln	Ala	Met	Leu	Asp	Ala	Leu	Val
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Met	Asp	Arg	Val	Ala	Phe	Val	Lys	Leu	Leu	Ile	Glu	Asn	Gly	Val	Ser
						455					460				
Met	His	Lys	Phe	Leu	Thr	Ile	Pro	Arg	Leu	Glu	Glu	Leu	Tyr	Asn	Thr
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Lys	Gln	Gly	Pro	Thr	Asn	Pro	Met	Leu	Phe	His	Leu	Val	Arg	Asp	Val
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Lys	Gln	Gly	Asn	Leu	Pro	Pro	Gly	Tyr	Lys	Ile	Thr	Leu	Ile	Asp	Ile
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Gly	Leu	Val	Ile	Glu	Tyr	Leu	Met	Gly	Gly	Thr	Tyr	Arg	Cys	Thr	Tyr
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Thr	Arg	Lys	Arg	Phe	Arg	Leu	Ile	Tyr	Asn	Ser	Leu	Gly	Gly	Asn	Asn
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Arg	Arg	Ser	Gly	Arg	Asn	Thr	Ser	Ser	Ser	Thr	Pro	Gln	Leu	Arg	Lys
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Ser	His	Glu	Ser	Phe	Gly	Asn	Arg	Ala	Asp	Lys	Lys	Glu	Lys	Met	Arg
				565					570						575
His	Asn	His	Phe	Ile	Lys	Thr	Ala	Gln	Pro	Phe	Arg	Pro	Lys	Ile	Asp
			580					585					590		
Thr	Val	Met	Glu	Glu	Gly	Lys	Lys	Arg	Thr	Lys	Asp	Glu	Ile	Val	
		595					600				605				
Asp	Ile	Asp	Asp	Pro	Glu	Thr	Lys	Arg	Phe	Pro	Tyr	Pro	Leu	Asn	Glu
	610					615					620				
Leu	Leu	Ile	Trp	Ala	Cys	Leu	Met	Lys	Arg	Gln	Val	Met	Ala	Arg	Phe
625					630					635					640
Leu	Trp	Gln	His	Gly	Glu	Glu	Ser	Met	Ala	Lys	Ala	Leu	Val	Ala	Cys
				645					650						655
Lys	Ile	Tyr	Arg	Ser	Met	Ala	Tyr	Glu	Ala	Lys	Gln	Ser	Asp	Leu	Val
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Asp	Asp	Thr	Ser	Glu	Glu	Leu	Lys	Gln	Tyr	Ser	Asn	Asp	Phe	Gly	Gln
		675					680					685			
Leu	Ala	Val	Glu	Leu	Leu	Glu	Gln	Ser	Phe	Arg	Gln	Asp	Glu	Thr	Met
		690				695					700				
Ala	Met	Lys	Leu	Leu	Thr	Tyr	Glu	Leu	Lys	Asn	Trp	Ser	Asn	Ser	Thr
705					710					715					720
Cys	Leu	Lys	Leu	Ala	Val	Ser	Ser	Arg	Leu	Arg	Pro	Phe	Val	Ala	His
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Thr	Cys	Thr	Gln	Met	Leu	Leu	Ser	Asp	Met	Trp	Met	Gly	Arg	Leu	Asn
			740					745					750		
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		755					760					765			
Pro	Ala	Ile	Leu	Leu	Leu	Glu	Tyr	Lys	Thr	Lys	Ala	Glu	Met	Ser	His
		770				775						780			
Ile	Pro	Gln	Ser	Gln	Asp	Ala	His	Gln	Met	Thr	Met	Asp	Asp	Ser	Glu
785					790					795					800
Asn	Asn	Phe	Gln	Asn	Ile	Thr	Glu	Glu	Ile	Pro	Met	Glu	Val	Phe	Lys
				805					810						815
Glu	Val	Arg	Ile	Leu	Asp	Ser	Asn	Glu	Gly	Lys	Asn	Glu	Met	Glu	Ile
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Gln	Met	Lys	Ser	Lys	Lys	Leu	Pro	Ile	Thr	Arg	Lys	Phe	Tyr	Ala	Phe
		835					840						845		

-43-

Tyr	His	Ala	Pro	Ile	Val	Lys	Phe	Trp	Phe	Asn	Thr	Leu	Ala	Tyr	Leu	850	855	860
Gly	Phe	Leu	Met	Leu	Tyr	Thr	Phe	Val	Val	Leu	Val	Gln	Met	Glu	Gln	865	870	875
Leu	Pro	Ser	Val	Gln	Glu	Trp	Ile	Val	Ile	Ala	Tyr	Ile	Phe	Thr	Tyr	885	890	895
Ala	Ile	Glu	Lys	Val	Arg	Glu	Ile	Phe	Met	Ser	Glu	Ala	Gly	Lys	Val	900	905	910
Asn	Gln	Lys	Ile	Lys	Val	Trp	Phe	Ser	Asp	Tyr	Phe	Asn	Ile	Ser	Asp	915	920	925
Thr	Ile	Ala	Ile	Ile	Ser	Phe	Phe	Ile	Gly	Phe	Gly	Leu	Arg	Phe	Gly	930	935	940
Ala	Lys	Trp	Asn	Phe	Ala	Asn	Ala	Tyr	Asp	Asn	His	Val	Phe	Val	Ala	945	950	955
Gly	Arg	Leu	Ile	Tyr	Cys	Leu	Asn	Ile	Ile	Phe	Trp	Tyr	Val	Arg	Leu	965	970	975
Leu	Asp	Phe	Leu	Ala	Val	Asn	Gln	Gln	Ala	Gly	Pro	Tyr	Val	Met	Met	980	985	990
Ile	Gly	Lys	Met	Val	Ala	Asn	Met	Phe	Tyr	Ile	Val	Val	Ile	Met	Ala	995	1000	1005
Leu	Val	Leu	Leu	Ser	Phe	Gly	Val	Pro	Arg	Lys	Ala	Ile	Leu	Tyr	Pro	1010	1015	1020
His	Glu	Ala	Pro	Ser	Trp	Thr	Leu	Ala	Lys	Asp	Ile	Val	Phe	His	Pro	1025	1030	1035
Tyr	Trp	Met	Ile	Phe	Gly	Glu	Val	Tyr	Ala	Tyr	Glu	Ile	Asp	Val	Cys	1045	1050	1055
Ala	Asn	Asp	Ser	Val	Ile	Pro	Gln	Ile	Cys	Gly	Pro	Gly	Thr	Trp	Leu	1060	1065	1070
Thr	Pro	Phe	Leu	Gln	Ala	Val	Tyr	Leu	Phe	Val	Gln	Tyr	Ile	Ile	Met	1075	1080	1085
Val	Asn	Leu	Leu	Ile	Ala	Phe	Phe	Asn	Asn	Val	Tyr	Leu	Gln	Val	Lys	1090	1095	1100
Ala	Ile	Ser	Asn	Ile	Val	Trp	Lys	Tyr	Gln	Arg	Tyr	His	Phe	Ile	Met	1105	1110	1115
Ala	Tyr	His	Glu	Lys	Pro	Val	Leu	Pro	Pro	Pro	Leu	Ile	Ile	Leu	Ser	1125	1130	1135
His	Ile	Val	Ser	Leu	Phe	Cys	Cys	Ile	Cys	Lys	Arg	Arg	Lys	Lys	Asp	1140	1145	1150
Lys	Thr	Ser	Asp	Gly	Pro	Lys	Leu	Phe	Leu	Thr	Glu	Glu	Asp	Gln	Lys	1155	1160	1165
Lys	Leu	His	Asp	Phe	Glu	Glu	Gln	Cys	Val	Glu	Met	Tyr	Phe	Asn	Glu	1170	1175	1180
Lys	Asp	Asp	Lys	Phe	His	Ser	Gly	Ser	Glu	Glu	Arg	Ile	Arg	Val	Thr	1185	1190	1195
Phe	Glu	Arg	Val	Glu	Gln	Met	Cys	Ile	Gln	Ile	Lys	Glu	Val	Gly	Asp	1205	1210	1215
Arg	Val	Asn	Tyr	Ile	Lys	Arg	Ser	Leu	Gln	Ser	Leu	Asp	Ser	Gln	Ile	1220	1225	1230
Gly	His	Leu	Gln	Asp	Leu	Ser	Ala	Leu	Thr	Val	Asp	Thr	Leu	Lys	Thr	1235	1240	1245
Leu	Thr	Ala	Gln	Lys	Ala	Ser	Glu	Ala	Ser	Lys	Val	His	Asn	Glu	Ile	1250	1255	1260
Thr	Arg	Glu	Leu	Ser	Ile	Ser	Lys	His	Leu	Ala	Gln	Asn	Leu	Ile	Asp	1265	1270	1275
Asp	Gly	Pro	Val	Arg	Pro	Ser	Val	Trp	Lys	Lys	His	Gly	Val	Val	Asn	1285	1290	1295
Thr	Leu	Ser	Ser	Ser	Leu	Pro	Gln	Gly	Asp	Leu	Glu	Ser	Asn	Asn	Pro	1300	1305	1310
Phe	His	Cys	Asn	Ile	Leu	Met	Lys	Asp	Asp	Lys	Asp	Pro	Gln	Cys	Asn	1315	1320	1325

-44-

Ile Phe Gly Gln Asp Leu Pro Ala Val Pro Gln Arg Lys Glu Phe Asn
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 Phe Pro Glu Ala Gly Ser Ser Ser Gly Ala Leu Phe Pro Ser Ala Val
 1345 1350 1355 1360
 Ser Pro Pro Glu Leu Arg Gln Arg Leu His Gly Val Glu Leu Leu Lys
 1365 1370 1375
 Ile Phe Asn Lys Asn Gln Lys Leu Gly Ser Ser Ser Thr Ser Ile Pro
 1380 1385 1390
 His Leu Ser Ser Pro Pro Thr Lys Phe Phe Val Ser Thr Pro Ser Gln
 1395 1400 1405
 Pro Ser Cys Lys Ser His Leu Glu Thr Gly Thr Lys Asp Gln Glu Thr
 1410 1415 1420
 Val Cys Ser Lys Ala Thr Glu Gly Asp Asn Thr Glu Phe Gly Ala Phe
 1425 1430 1435 1440
 Val Gly His Arg Asp Ser Met Asp Leu Gln Arg Phe Lys Glu Thr Ser
 1445 1450 1455
 Asn Lys Ile Lys Ile Leu Ser Asn Asn Asn Thr Ser Glu Asn Thr Leu
 1460 1465 1470
 Lys Arg Val Ser Ser Leu Ala Gly Phe Thr Asp Cys His Arg Thr Ser
 1475 1480 1485
 Ile Pro Val His Ser Lys Gln Ala Glu Lys Ile Ser Arg Arg Pro Ser
 1490 1495 1500
 Thr Glu Asp Thr His Glu Val Asp Ser Lys Ala Ala Leu Ile Pro Asp
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 Trp Leu Gln Asp Arg Pro Ser Asn Arg Glu Met Pro Ser Glu Glu Gly
 1525 1530 1535
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 1570 1575 1580
 Tyr Arg Leu Glu Glu Ser Ser Pro Asn Ile Leu Asn Asn Ser Met Ser
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 1650 1655 1660
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 Pro Tyr Ser Pro Arg Phe Leu Glu Val Phe Leu Leu Tyr Cys His Ser
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 Lys Tyr Asn Asn Asn Asn Gly Asp Glu Ile Ile Pro Thr Asn Thr Leu
 1730 1735 1740
 Glu Glu Ile Met Leu Ala Phe Ser His Trp Thr Tyr Glu Tyr Thr Arg
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 Gly Glu Leu Leu Val Leu Asp Leu Gln Gly Val Gly Glu Asn Leu Thr
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 Asp Pro Ser Val Ile Lys Ala Glu Glu Lys Arg Ser Cys Asp Met Val
 1780 1785 1790
 Phe Gly Pro Ala Asn Leu Gly Glu Asp Ala Ile Lys Asn Phe Arg Ala
 1795 1800 1805

-45-

Lys His His Cys Asn Ser Cys Cys Arg Lys Leu Lys Leu Pro Asp Leu
 1810 1815 1820
 Lys Arg Asn Asp Tyr Thr Pro Asp Lys Ile Ile Phe Pro Gln Asp Glu
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-46-

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 <211> 1214
 <212> PRT
 <213> Homo Sapiens

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Lys Lys Thr Cys Thr Thr Phe Ile Val Asp Ser Thr Asp Pro Gly Gly
 20          25          30
Thr Leu Cys Gln Cys Gly Arg Pro Arg Thr Ala His Pro Ala Val Ala
 35          40          45
Met Glu Asp Ala Phe Gly Ala Ala Val Val Thr Val Trp Asp Ser Asp
 50          55          60
Ala His Thr Thr Glu Lys Pro Thr Asp Ala Tyr Gly Glu Leu Asp Phe
 65          70          75          80
Thr Gly Ala Gly Arg Lys His Ser Asn Phe Leu Arg Leu Ser Asp Arg
 85          90          95
Thr Asp Pro Ala Ala Val Tyr Ser Leu Val Thr Arg Thr Trp Gly Phe
100          105          110
Arg Ala Pro Asn Leu Val Val Ser Val Leu Gly Gly Ser Gly Gly Pro
115          120          125
Val Leu Gln Thr Trp Leu Gln Asp Leu Leu Arg Arg Gly Leu Val Arg
130          135          140
Ala Ala Gln Ser Thr Gly Ala Trp Ile Val Thr Gly Gly Leu His Thr
145          150          155          160
Gly Ile Gly Arg His Val Gly Val Ala Val Arg Asp His Gln Met Ala
165          170          175
Ser Thr Gly Gly Thr Lys Val Val Ala Met Gly Val Ala Pro Trp Gly
180          185          190
Val Val Arg Asn Arg Asp Thr Leu Ile Asn Pro Lys Gly Ser Phe Pro
195          200          205
Ala Arg Tyr Arg Trp Arg Gly Asp Pro Glu Asp Gly Val Gln Phe Pro
210          215          220
Leu Asp Tyr Asn Tyr Ser Ala Phe Phe Leu Val Asp Asp Gly Thr His
225          230          235          240

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-47-

Gly	Cys	Leu	Gly	Gly	Glu	Asn	Arg	Phe	Arg	Leu	Arg	Leu	Glu	Ser	Tyr	245	250	255
Ile	Ser	Gln	Gln	Lys	Thr	Gly	Val	Gly	Gly	Thr	Gly	Ile	Asp	Ile	Pro	260	265	270
Val	Leu	Leu	Leu	Leu	Ile	Asp	Gly	Asp	Glu	Lys	Met	Leu	Thr	Arg	Ile	275	280	285
Glu	Asn	Ala	Thr	Gln	Ala	Gln	Leu	Pro	Cys	Leu	Leu	Val	Ala	Gly	Ser	290	295	300
Gly	Gly	Ala	Ala	Asp	Cys	Leu	Ala	Glu	Thr	Leu	Glu	Asp	Thr	Leu	Ala	305	310	315
Pro	Gly	Ser	Gly	Gly	Ala	Arg	Gln	Gly	Glu	Ala	Arg	Asp	Arg	Ile	Arg	325	330	335
Arg	Phe	Phe	Pro	Lys	Gly	Asp	Leu	Glu	Val	Leu	Gln	Ala	Gln	Val	Glu	340	345	350
Arg	Ile	Met	Thr	Arg	Lys	Glu	Leu	Leu	Thr	Val	Tyr	Ser	Ser	Glu	Asp	355	360	365
Gly	Ser	Glu	Glu	Phe	Glu	Thr	Ile	Val	Leu	Lys	Ala	Leu	Val	Lys	Ala	370	375	380
Cys	Gly	Ser	Ser	Glu	Ala	Ser	Ala	Tyr	Leu	Asp	Glu	Leu	Arg	Leu	Ala	385	390	395
Val	Ala	Trp	Asn	Arg	Val	Asp	Ile	Ala	Gln	Ser	Glu	Leu	Phe	Arg	Gly	405	410	415
Asp	Ile	Gln	Trp	Arg	Ser	Phe	His	Leu	Glu	Ala	Ser	Leu	Met	Asp	Ala	420	425	430
Leu	Leu	Asn	Asp	Arg	Pro	Glu	Phe	Val	Arg	Leu	Leu	Ile	Ser	His	Gly	435	440	445
Leu	Ser	Leu	Gly	His	Phe	Leu	Thr	Pro	Met	Arg	Leu	Ala	Gln	Leu	Tyr	450	455	460
Ser	Ala	Ala	Pro	Ser	Asn	Ser	Leu	Ile	Arg	Asn	Leu	Leu	Asp	Gln	Ala	465	470	475
Ser	His	Ser	Ala	Gly	Thr	Lys	Ala	Pro	Ala	Leu	Lys	Gly	Gly	Ala	Ala	485	490	495
Glu	Leu	Arg	Pro	Pro	Asp	Val	Gly	His	Val	Leu	Arg	Met	Leu	Leu	Gly	500	505	510
Lys	Met	Cys	Ala	Pro	Arg	Tyr	Pro	Ser	Gly	Gly	Ala	Trp	Asp	Pro	His	515	520	525
Pro	Gly	Gln	Gly	Phe	Gly	Glu	Ser	Met	Tyr	Leu	Leu	Ser	Asp	Lys	Ala	530	535	540
Thr	Ser	Pro	Leu	Ser	Leu	Asp	Ala	Gly	Leu	Gly	Gln	Ala	Pro	Trp	Ser	545	550	555
Asp	Leu	Leu	Leu	Trp	Ala	Leu	Leu	Leu	Asn	Arg	Ala	Gln	Met	Ala	Met	565	570	575
Tyr	Phe	Trp	Glu	Met	Gly	Ser	Asn	Ala	Val	Ser	Ser	Ala	Leu	Gly	Ala	580	585	590
Cys	Leu	Leu	Leu	Arg	Val	Met	Ala	Arg	Leu	Glu	Pro	Asp	Ala	Glu	Glu	595	600	605
Ala	Ala	Arg	Arg	Lys	Asp	Leu	Ala	Phe	Lys	Phe	Glu	Gly	Met	Gly	Val	610	615	620
Asp	Leu	Phe	Gly	Glu	Cys	Tyr	Arg	Ser	Ser	Glu	Val	Arg	Ala	Ala	Arg	625	630	635
Leu	Leu	Leu	Arg	Arg	Cys	Pro	Leu	Trp	Gly	Asp	Ala	Thr	Cys	Leu	Gln	645	650	655
Leu	Ala	Met	Gln	Ala	Asp	Ala	Arg	Ala	Phe	Phe	Ala	Gln	Asp	Gly	Val	660	665	670
Gln	Ser	Leu	Leu	Thr	Gln	Lys	Trp	Trp	Gly	Asp	Met	Ala	Ser	Thr	Thr	675	680	685
Pro	Ile	Trp	Ala	Leu	Val	Leu	Ala	Phe	Phe	Cys	Pro	Pro	Leu	Ile	Tyr	690	695	700
Thr	Arg	Leu	Ile	Thr	Phe	Arg	Lys	Ser	Glu	Glu	Glu	Pro	Thr	Arg	Glu	705	710	715
																		720

-48-

Glu Leu Glu Phe Asp Met Asp Ser Val Ile Asn Gly Glu Gly Pro Val
 725 730 735
 Gly Thr Ala Asp Pro Ala Glu Lys Thr Pro Leu Gly Val Pro Arg Gln
 740 745 750
 Ser Gly Arg Pro Gly Cys Cys Gly Gly Arg Cys Gly Gly Arg Arg Cys
 755 760 765
 Leu Arg Arg Trp Phe His Phe Trp Gly Ala Pro Val Thr Ile Phe Met
 770 775 780
 Gly Asn Val Val Ser Tyr Leu Leu Phe Leu Leu Phe Ser Arg Val
 785 790 795 800
 Leu Leu Val Asp Phe Gln Pro Ala Pro Pro Gly Ser Leu Glu Leu Leu
 805 810 815
 Leu Tyr Phe Trp Ala Phe Thr Leu Leu Cys Glu Glu Leu Arg Gln Gly
 820 825 830
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 835 840 845
 His Ala Ser Leu Ser Gln Arg Leu Arg Leu Tyr Leu Ala Asp Ser Trp
 850 855 860
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 Cys Arg Leu Thr Pro Gly Leu Tyr His Leu Gly Arg Thr Val Leu Cys
 885 890 895
 Ile Asp Phe Met Val Phe Thr Val Arg Leu Leu His Ile Phe Thr Val
 900 905 910
 Asn Lys Gln Leu Gly Pro Lys Ile Val Ile Val Ser Lys Met Met Lys
 915 920 925
 Asp Val Phe Phe Phe Leu Phe Phe Leu Gly Val Trp Leu Val Ala Tyr
 930 935 940
 Gly Val Ala Thr Glu Gly Leu Leu Arg Pro Arg Asp Ser Asp Phe Pro
 945 950 955 960
 Ser Ile Leu Arg Arg Val Phe Tyr Arg Pro Tyr Leu Gln Ile Phe Gly
 965 970 975
 Gln Ile Pro Gln Glu Asp Met Asp Val Ala Leu Met Glu His Ser Asn
 980 985 990
 Cys Ser Ser Glu Pro Gly Phe Trp Ala His Pro Pro Gly Ala Gln Ala
 995 1000 1005
 Gly Thr Cys Val Ser Gln Tyr Ala Asn Trp Leu Val Val Leu Leu Leu
 1010 1015 1020
 Val Ile Phe Leu Leu Val Ala Asn Ile Leu Leu Val Asn Leu Leu Ile
 1025 1030 1035 1040
 Ala Met Phe Ser Tyr Thr Phe Gly Lys Val Gln Gly Asn Ser Asp Leu
 1045 1050 1055
 Tyr Trp Lys Ala Gln Arg Tyr Arg Leu Ile Arg Glu Phe His Ser Arg
 1060 1065 1070
 Pro Ala Leu Ala Pro Pro Phe Ile Val Ile Ser His Leu Arg Leu Leu
 1075 1080 1085
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 1090 1095 1100
 Ala Leu Glu His Phe Arg Val Tyr Leu Ser Lys Glu Ala Glu Arg Lys
 1105 1110 1115 1120
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 1125 1130 1135
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 1140 1145 1150
 Gln Lys Val Asp Leu Ala Leu Lys Gln Leu Gly His Ile Arg Glu Tyr
 1155 1160 1165
 Glu Gln Arg Leu Lys Val Leu Glu Arg Glu Val Gln Gln Cys Ser Arg
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<213> Homo Sapiens

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-50-

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<211> 1104

<212> PRT

<213> Homo Sapiens

<400> 32

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20      25      30
Asp Leu Ser Tyr Ser Glu Ser Asp Leu Val Asn Phe Ile Gln Ala Asn
35      40      45
Phe Lys Lys Arg Glu Cys Val Phe Phe Thr Lys Asp Ser Lys Ala Thr
50      55      60
Glu Asn Val Cys Lys Cys Gly Tyr Ala Gln Ser Gln His Met Glu Gly
65      70      75      80
Thr Gln Ile Asn Gln Ser Glu Lys Trp Asn Tyr Lys Lys His Thr Lys
85      90      95
Glu Phe Pro Thr Asp Ala Phe Gly Asp Ile Gln Phe Glu Thr Leu Gly
100     105     110
Lys Lys Gly Lys Tyr Ile Arg Leu Ser Cys Asp Thr Asp Ala Glu Ile
115     120     125
Leu Tyr Glu Leu Leu Thr Gln His Trp His Leu Lys Thr Pro Asn Leu
130     135     140
Val Ile Ser Val Thr Gly Gly Ala Lys Asn Phe Ala Leu Lys Pro Arg
145     150     155     160
Met Arg Lys Ile Phe Ser Arg Leu Ile Tyr Ile Ala Gln Ser Lys Gly
165     170     175
Ala Trp Ile Leu Thr Gly Gly Thr His Tyr Gly Leu Met Lys Tyr Ile
180     185     190
Gly Glu Val Val Arg Asp Asn Thr Ile Ser Arg Ser Ser Glu Glu Asn
195     200     205

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-51-

Ile	Val	Ala	Ile	Gly	Ile	Ala	Ala	Trp	Gly	Met	Val	Ser	Asn	Arg	Asp	210	215	220
Thr	Leu	Ile	Arg	Asn	Cys	Asp	Ala	Glu	Gly	Tyr	Phe	Leu	Ala	Gln	Tyr	225	230	235
Leu	Met	Asp	Asp	Phe	Thr	Arg	Asp	Pro	Leu	Cys	Ile	Leu	Asp	Asn	Asn	245	250	255
His	Thr	His	Leu	Leu	Leu	Val	Asp	Asn	Gly	Cys	His	Gly	His	Pro	Thr	260	265	270
Val	Glu	Ala	Lys	Leu	Arg	Asn	Gln	Leu	Glu	Lys	Tyr	Ile	Ser	Glu	Arg	275	280	285
Thr	Ile	Gln	Asp	Ser	Asn	Tyr	Gly	Gly	Lys	Ile	Pro	Ile	Val	Cys	Phe	290	295	300
Ala	Gln	Gly	Gly	Gly	Lys	Glu	Thr	Leu	Lys	Ala	Ile	Asn	Thr	Ser	Ile	305	310	315
Lys	Asn	Lys	Ile	Pro	Cys	Val	Val	Val	Glu	Gly	Ser	Gly	Gln	Ile	Ala	325	330	335
Asp	Val	Ile	Ala	Ser	Leu	Val	Glu	Val	Glu	Asp	Ala	Leu	Thr	Ser	Ser	340	345	350
Ala	Val	Lys	Glu	Lys	Leu	Val	Arg	Phe	Leu	Pro	Arg	Thr	Val	Ser	Arg	355	360	365
Leu	Pro	Glu	Glu	Glu	Thr	Glu	Ser	Trp	Ile	Lys	Trp	Leu	Lys	Glu	Ile	370	375	380
Leu	Glu	Cys	Ser	His	Leu	Leu	Thr	Val	Ile	Lys	Met	Glu	Glu	Ala	Gly	385	390	395
Asp	Glu	Ile	Val	Ser	Asn	Ala	Ile	Ser	Tyr	Ala	Leu	Tyr	Lys	Ala	Phe	405	410	415
Ser	Thr	Ser	Glu	Gln	Asp	Lys	Asp	Asn	Trp	Asn	Gly	Gln	Leu	Lys	Leu	420	425	430
Leu	Leu	Glu	Trp	Asn	Gln	Leu	Asp	Leu	Ala	Asn	Asp	Glu	Ile	Phe	Thr	435	440	445
Asn	Asp	Arg	Arg	Trp	Glu	Ser	Ala	Asp	Leu	Gln	Glu	Val	Met	Phe	Thr	450	455	460
Ala	Leu	Ile	Lys	Asp	Arg	Pro	Lys	Phe	Val	Arg	Leu	Phe	Leu	Glu	Asn	465	470	475
Gly	Leu	Asn	Leu	Arg	Lys	Phe	Leu	Thr	His	Asp	Val	Leu	Thr	Glu	Leu	485	490	495
Phe	Ser	Asn	His	Phe	Ser	Thr	Leu	Val	Tyr	Arg	Asn	Leu	Gln	Ile	Ala	500	505	510
Lys	Asn	Ser	Tyr	Asn	Asp	Ala	Leu	Leu	Thr	Phe	Val	Trp	Lys	Leu	Val	515	520	525
Ala	Asn	Phe	Arg	Arg	Gly	Phe	Arg	Lys	Glu	Asp	Arg	Asn	Gly	Arg	Asp	530	535	540
Glu	Met	Asp	Ile	Glu	Leu	His	Asp	Val	Ser	Pro	Ile	Thr	Arg	His	Pro	545	550	555
Leu	Gln	Ala	Leu	Phe	Ile	Trp	Ala	Ile	Leu	Gln	Asn	Lys	Lys	Glu	Leu	565	570	575
Ser	Lys	Val	Ile	Trp	Glu	Gln	Thr	Arg	Gly	Cys	Thr	Leu	Ala	Ala	Leu	580	585	590
Gly	Ala	Ser	Lys	Leu	Leu	Lys	Thr	Leu	Ala	Lys	Val	Lys	Asn	Asp	Ile	595	600	605
Asn	Ala	Ala	Gly	Glu	Ser	Glu	Glu	Leu	Ala	Asn	Glu	Tyr	Glu	Thr	Arg	610	615	620
Ala	Val	Glu	Leu	Phe	Thr	Glu	Cys	Tyr	Ser	Ser	Asp	Glu	Asp	Leu	Ala	625	630	635
Glu	Gln	Leu	Leu	Val	Tyr	Ser	Cys	Glu	Ala	Trp	Gly	Gly	Ser	Asn	Cys	645	650	655
Leu	Glu	Leu	Ala	Val	Glu	Ala	Thr	Asp	Gln	His	Phe	Ile	Ala	Gln	Pro	660	665	670
Gly	Val	Gln	Asn	Phe	Leu	Ser	Lys	Gln	Trp	Tyr	Gly	Glu	Ile	Ser	Arg	675	680	685

-52-

Asp	Thr	Lys	Asn	Trp	Lys	Ile	Ile	Leu	Cys	Leu	Phe	Ile	Ile	Pro	Leu
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Lys	Lys	Leu	Leu	Trp	Tyr	Tyr	Val	Ala	Phe	Phe	Thr	Ser	Pro	Phe	Val
				725					730					735	
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Ala	Tyr	Val	Leu	Leu	Met	Asp	Phe	His	Ser	Val	Pro	His	Pro	Pro	Glu
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Leu	Val	Leu	Tyr	Ser	Leu	Val	Phe	Val	Leu	Phe	Cys	Asp	Glu	Val	Arg
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Gln	Trp	Tyr	Val	Asn	Gly	Val	Asn	Tyr	Phe	Thr	Asp	Leu	Trp	Asn	Val
785					790					795					800
Met	Asp	Thr	Leu	Gly	Leu	Phe	Tyr	Phe	Ile	Ala	Gly	Ile	Val	Phe	Arg
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Cys	Leu	Asp	Tyr	Ile	Ile	Phe	Thr	Leu	Arg	Leu	Ile	His	Ile	Phe	Thr
		835					840					845			
Val	Ser	Arg	Asn	Leu	Gly	Pro	Lys	Ile	Ile	Met	Leu	Gln	Arg	Met	Leu
		850				855					860				
Ile	Asp	Val	Phe	Phe	Phe	Leu	Phe	Leu	Phe	Ala	Val	Trp	Met	Val	Ala
865					870					875					880
Phe	Gly	Val	Ala	Arg	Gln	Gly	Ile	Leu	Arg	Gln	Asn	Glu	Gln	Arg	Trp
			885						890					895	
Arg	Trp	Ile	Phe	Arg	Ser	Val	Ile	Tyr	Glu	Pro	Tyr	Leu	Ala	Met	Phe
			900					905					910		
Gly	Gln	Val	Pro	Ser	Asp	Val	Asp	Gly	Thr	Thr	Tyr	Asp	Phe	Ala	His
		915					920					925			
Cys	Thr	Phe	Thr	Gly	Asn	Glu	Ser	Lys	Pro	Leu	Cys	Val	Glu	Leu	Asp
		930				935					940				
Glu	His	Asn	Leu	Pro	Arg	Phe	Pro	Glu	Trp	Ile	Thr	Ile	Pro	Leu	Val
945					950					955					960
Cys	Ile	Tyr	Met	Leu	Ser	Thr	Asn	Ile	Leu	Val	Asn	Leu	Leu	Val	
			965						970					975	
Ala	Met	Phe	Gly	Tyr	Thr	Val	Gly	Thr	Val	Gln	Glu	Asn	Asn	Asp	Gln
			980					985					990		
Val	Trp	Lys	Phe	Gln	Arg	Tyr	Phe	Leu	Val	Gln	Glu	Tyr	Cys	Ser	Arg
		995					1000					1005			
Leu	Asn	Ile	Pro	Phe	Pro	Phe	Ile	Val	Phe	Ala	Tyr	Phe	Tyr	Met	Val
		1010				1015						1020			
Val	Lys	Lys	Cys	Phe	Lys	Cys	Cys	Cys	Lys	Glu	Lys	Asn	Met	Glu	Ser
1025					1030					1035					104
Ser	Val	Cys	Cys	Phe	Lys	Asn	Glu	Asp	Asn	Glu	Thr	Leu	Ala	Trp	Glu
				1045					1050					1055	
Gly	Val	Met	Lys	Glu	Asn	Tyr	Leu	Val	Lys	Ile	Asn	Thr	Lys	Ala	Asn
			1060					1065					1070		
Asp	Thr	Ser	Glu	Glu	Met	Arg	His	Arg	Phe	Arg	Gln	Leu	Asp	Thr	Lys
		1075					1080					1085			
Leu	Asn	Asp	Leu	Lys	Gly	Leu	Leu	Lys	Glu	Ile	Ala	Asn	Lys	Ile	Lys
		1090				1095						1100			

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/29996

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07K14/705 C12N15/12 C12Q1/68 C12N5/10 C07K16/28 G01N33/53 A61K38/17		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C12N C07K C12Q A61K G01N		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) BIOSIS, EPO-Internal, WPI Data, PAJ, MEDLINE, SCISEARCH, EMBASE, BIOTECHNOLOGY ABS, CHEM ABS Data, STRAND, GENSEQ, EMBL		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE GENEMBL 'Online! 16 February 1998 (1998-02-16) STRAUSBERG, R.: "ob70f05.s1 NCI_CGAP_GCB1 Homo sapiens cDNA clone IMAGE:1336737 3', mRNA sequence" XP002138823 Accession AA809355	1,2, 6-19, 25-35
X	DATABASE GENEMBL 'Online! 10 July 1998 (1998-07-10) MARRA ET AL.: "ub28d10.r1 Soares 2NbMT Mus musculus cDNA clone IMAGE:1379059 5' mRNA sequence" XP002149803 Accession AI050262	1,6-19, 25-35
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		
<input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents: <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*Z* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-size: 1.2em;">16 October 2000</div>		Date of mailing of the international search report <div style="text-align: center; font-size: 1.2em;">30. 10. 00</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-size: 1.2em;">ALCONADA RODRIG..., A</div>

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/US 99/29996

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE GENEMBL 'Online! 19 July 1997 (1997-07-19) STRAUSBERG, R.: "ni64e11.s1 NCI_CGAP_Pr12 Homo sapiens cDNA clone IMAGE:981644 mRNA sequence" XP002148641 Accession AA523749 ---	1,3, 10-19, 25-35
X	WO 98 15657 A (ABBOTT LAB) 16 April 1998 (1998-04-16) page 4, line 7 -page 5, line 13 page 5, line 24 -page 7, line 28	1,4, 6-19, 25-35
Y	SEQ ID NOs. 9 and 25 ---	20-24
X	WO 98 37093 A (CORIXA CORP) 27 August 1998 (1998-08-27) page 7, paragraph 2 page 9, paragraphs 2,3 page 13 -page 17 page 21, paragraph 3	1,4, 6-19, 25-35
Y	SEQ ID NOs: 109 and 112 ---	20-24
X	DATABASE GENEMBL 'Online! 18 November 1997 (1997-11-18) STRAUSBERG, R.: "nt76b07.s1 NCI_CGAP_Pr3 Homo sapiens cDNA clone IMAGE:1204405, mRNA" XP002148642 Accession AA654650 ---	1,5-19, 25-35
Y	---	20-24
Y	DATABASE GENEMBL 'Online! 30 November 1998 (1998-11-30) SHIMIZU, N.: "Homo sapiens mRNA complete cds." XP002148643 Accession number AB001535 -& NAGAMINE ET AL.: "Molecular cloning of a novel putative Ca ²⁺ channel protein (TRPC7) highly expressed in brain" GENOMICS, vol. 54, 15 November 1998 (1998-11-15), pages 124-131, XP000938744 the whole document --- -/--	20-24

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/29996

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ZHU, XI ET AL: "Molecular cloning of a widely expressed human homologue for the <i>Drosophila</i> trp gene." FEBS LETTERS, (1995) VOL. 373, NO. 3, PP. 193-198., XP000907241 page 194; figures 1,3</p> <p style="text-align: center;">---</p>	<p>20,21, 23,25, 26,28, 29,31</p>
A	<p>HUNTER JOHN J ET AL: "Chromosomal localization and genomic characterization of the mouse melastatin gene (<i>Mln1</i>)." GENOMICS NOV. 15, 1998, vol. 54, no. 1, 15 November 1998 (1998-11-15), pages 116-123, XP000910696 ISSN: 0888-7543 cited in the application page 119; figure 2</p> <p style="text-align: center;">---</p>	<p>20,21,23</p>
A	<p>WES PAUL D ET AL: "TRPC1, a human homolog of a <i>Drosophila</i> store-operated channel." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 1995, vol. 92, no. 21, 1995, pages 9652-9656, XP002138820 ISSN: 0027-8424 the whole document</p> <p style="text-align: center;">---</p>	<p>20,21, 23,25, 26,28, 29,31</p>
A	<p>ZHU, XI ET AL: "Trp, A novel mammalian gene family essential for agonist-activated capacitative Ca-2+ entry." CELL, vol. 85, no. 5, 1996, pages 661-671, XP000907242 page 662 page 665 figures 1,5,6</p> <p style="text-align: center;">---</p>	<p>20,21, 25,26, 28,29,31</p>
A	<p>GARCIA REYNALDO L ET AL: "Differential expression of mammalian TRP homologues across tissues and cell lines." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS 1997, vol. 239, no. 1, 1997, pages 279-283, XP002138822 ISSN: 0006-291X See Materials and Methods figure 1</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	<p>25,26, 28-30</p>

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/29996

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>SINKINS WILLIAM G ET AL: "Functional expression of TrpCl: A human homologue of the Drosophila Trp channel." BIOCHEMICAL JOURNAL APRIL, 1998, vol. 331, no. 1, April 1998 (1998-04), pages 331-339, XP000864583 ISSN: 0264-6021 page 333-335; figures 3-5</p>	24
A	<p>PREUSS KLAUS-DIETER ET AL: "Expression and characterization of a trpl homolog from rat." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS NOV. 7, 1997, vol. 240, no. 1, 7 November 1997 (1997-11-07), pages 167-172, XP002138821 ISSN: 0006-291X figure 2</p>	24
A	<p>OBUKHOV, ALEXANDER G. ET AL: "Direct activation of trpl cation channels by G-alpha-11 subunits." EMBO (EUROPEAN MOLECULAR BIOLOGY ORGANIZATION) JOURNAL, (1996) VOL. 15, NO. 21, PP. 5833-5838., XP000907243 figure 2</p>	24
P,X	<p>WO 99 09199 A (RYAZANOV ALEXEY G ;PAVUR KAREN S (US); HAIT WILLIAM N (US); UNIV M) 25 February 1999 (1999-02-25) see melanome kinase polynucleotide and polypeptide sequences on page 16-17</p>	1,3, 10-19, 25-36
P,X	<p>WO 99 09166 A (SHAPERO MICHAEL H ;DENDREON CORP (US); LAUS REINER (US); TSAVALER) 25 February 1999 (1999-02-25) page 17, line 24 -page 18, line 9 page 25, line 19-32 page 28, line 1-4 SEQ ID NOs: 27, 28 and 31.</p>	1,5-19, 25-35
T	<p>SCHARENBERG A M ET AL: "MLSN-1/SOC-1 defines a widely expressed Ca2+/cation channel family involved in Ca2+ homeostasis and store-operated Ca2+ signaling." FIFTY-THIRD ANNUAL MEETING OF THE SOCIETY OF GENERAL PHYSIOLOGISTS;WOODS HOLE, MASSACHUSETTS, USA; SEPTEMBER 9-11, 1999, vol. 114, no. 1, July 1999 (1999-07), page 14a XP000910708 Journal of General Physiology July, 1999 ISSN: 0022-1295</p>	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/29996

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,
no additional fees are to be refunded.

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
1-36
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-5, 10-13, 16-19, 32-35 relate to an extremely large number of possible polynucleotides, polypeptides encoded by them, binding polypeptides, and kits and pharmaceutical compositions containing said polypeptides and polynucleotides. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the polynucleotide of SEQ ID NOs: 1, 27, 29 and 31 and the corresponding polypeptide of SEQ ID NOs: 2, 28, 30 and 32.

Present claims 16 and 17 relate to an extremely large number of possible compounds, namely, a polypeptide that binds to the polypeptide of the invention. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to an antibody, antibody fragment, F(ab)2 fragment or a fragment including a CDR3 region selective for the polypeptides of the invention.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1, 6-36 (partially) and 2 (complete)

An isolated nucleic acid molecule comprising a nucleic acid molecule that hybridizes to a nucleic acid molecule of SEQ ID NO:1 and which code for a SOC/CRAC polypeptide, nucleic acid molecules that differ in codon sequence due to degeneracy of the genetic code and complement thereof, polynucleotides which are not identical to the SEQ ID or sequences of GenBank accession number of Table 1; expression vector, host cells; polypeptide encoded thereof (SEQ ID NO:2); polypeptides binding to the polypeptide of SEQ ID NO:2, including antibodies; kits comprising agents that selectively bind to the polynucleotide (SEQ ID NO:1) or polypeptide (SEQ ID NO:2) of the invention; pharmaceutical compositions containing the polynucleotide or polypeptides of the invention; a method for isolating the SOC/CRAC molecule having SOC/CRAC calcium channel activity comprising contacting a binding molecule that is SOC/CRAC nucleic acid or a SOC/CRAC binding polypeptide with a sample containing SOC/CRAC molecules allowing the formation of the complex, detecting the formation of the complex, isolating the SOC/CRAC molecule and determining whether the isolated SOC/CRAC molecule has SOC/CRAC calcium channel activity; a method for identifying agents useful in the modulation of SOC/CRAC calcium channel activity; a method to determine the level of SOC/CRAC expression in a subject, including expression of SOC/CRAC polypeptide or mRNA in a tissue or biological fluid sample using PCR, Northern blotting, and mono- and polyclonal antisera and a method for identifying agents useful in the modulation of the SOC/CRAC polypeptide kinase activity, comprising the use of aminoacids 999-1180 from SEQ ID NO:4 as a candidate kinase.

2. Claims: 1,6-36 (partially)

As subject 1, but referred to the polynucleotide of SEQ ID NO:3 and to the encoded polypeptide of SEQ ID NO:4

3. Claims: 1,6-36 (partially)

As subject 1, but referred to the polynucleotide of SEQ ID NO:5 and to the encoded polypeptide of SEQ ID NO:6

4. Claims: 1,6-36 (partially)

As subject 1, but referred to the polynucleotide of SEQ ID NO:7 and to the encoded polypeptide of SEQ ID NO:8

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

5. Claims: 1,6-36 (partially) and 37 (complete)

As subject 1, but referred to the polynucleotide of SEQ ID NO:23 and to the encoded polypeptide of SEQ ID NO:24

6. Claims: 1,6-36 (partially)

As subject 1, but referred to the polynucleotide of SEQ ID NO:25 and to the encoded polypeptide of SEQ ID NO:26

7. Claims: 1,10-36 (partially) and 3 (complete)

As subject 1, but referred to the polynucleotide of SEQ ID NO:27 and to the encoded polypeptide of SEQ ID NO:28

8. Claims: 1,6-36 (partially) and 4 (complete)

As subject 1, but referred to the polynucleotide of SEQ ID NO:29 and to the encoded polypeptide of SEQ ID NO:30

9. Claims: 1,6-36 (partially) and 5 (complete)

As subject 1, but referred to the polynucleotide of SEQ ID NO:31 and to the encoded polypeptide of SEQ ID NO:32.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/US 99/29996

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9815657 A	16-04-1998	US 5919638 A EP 0954599 A US 6110675 A	06-07-1999 10-11-1999 29-08-2000
WO 9837093 A	27-08-1998	AU 6181898 A CN 1252837 T EP 1005546 A NO 994069 A PL 335348 A ZA 9801585 A	09-09-1998 10-05-2000 07-06-2000 22-10-1999 25-04-2000 04-09-1998
WO 9909199 A	25-02-1999	AU 9110098 A	08-03-1999
WO 9909166 A	25-02-1999	AU 9021898 A EP 1005549 A	08-03-1999 07-06-2000